The Validity of Skin Conductance for Pain Assessment in Hospitalized Infants

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Abstract

Background

Measuring pain in infants is important but challenging for researchers and health care professionals. The measurement of skin conductance (SC) is considered as a measure of stress and a surrogate indicator of pain.

Purpose

This dissertation provides insight on the validity of SC for pain measurement in infants and consists of two studies: 1) a scoping review synthesizing the methods and findings of previous studies on validating or using SC for measuring pain in infants; 2) a primary study evaluating the validity of SC for measuring pain in mechanically ventilated infants.

Methods

Arksey and O'Malley's framework informed the methods of the scoping review. Nine electronic databases were searched. Data were analyzed and presented descriptively. The primary study used a prospective cross-sectional observational design. Eligible infants were those up to 12 months of age, hospitalized in intensive care units, who were mechanically ventilated, and required painful and non-painful procedures.

Results

Scoping review: Twenty-eight studies with 1061 infants were included, including 23 cross-sectional observation studies and five interventional studies. The validity evidence of SC was tested in relation to referent pain measures (13 variables), stimuli (13 variables), age (2 variables) and other contextual variables (11 variables). Fifteen studies evaluated the

validity evidence in relation to phase of painful procedure, and SC increased significantly during painful procedures in most studies (n=14/15). However, inconsistent findings on other validity evidence and wide variation in methods existed across studies.

Primary study: SC showed good validity in relation to the category of procedure, the phase of procedure and the referent pain measures in critically ill mechanically ventilated infants. The findings from diagnostic test accuracy showed that SC had good capacity of detecting moderate to severe pain. However, the values of SC need to be used with caution, due to the imperfect correlations with the referent pain measures and imperfect positive predictive value.

Conclusions

SC is a promising approach to measuring pain in critically ill infants. Further research testing the validity of SC in relation to pain treatments and advancing the technology of measuring and analyzing SC is needed before it can be recommended for clinical use.

Dedication

This dissertation is dedicated to my wife Yiyan Zhou. Without your tireless support I believe I would not have made through the daunting task to completing this PhD. I do not know what I would do without you.

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Abbreviations

AERA	American Educational Research Association
COMFORT-b	COMFORT behavioural scale
EEG	Electro-encephalography
FLACC	Face, Legs, Activity, Cry and Consolability scale
fMRI	Functional magnetic resonance imaging
HCPs	Health care professionals
IASP	International Association for the Study of Pain
IQR	Interquartile range
NFCS	Neonatal Facial Coding System
NICU	Neonatal intensive care unit
NIRS	Near-infrared spectroscopy
NTISS	Neonatal Therapeutic Intervention Scoring System
NWps	Number of waves per second
PACU	Post-anesthesia care unit
PICU	Pediatric intensive care unit
PIPP	Premature Infant Pain Profile
PIPP-R	Premature Infant Pain Profile-Revised
RNAO	Registered Nurses' Association of Ontario
ROC	Receiver operator curve
SC	Skin conductance

SID	Subject Identification Number
USA	United States of America
VAS	Visual analog scale
VASobs	Observational visual analog scale

Chapter 1: Introduction

The overall purpose of this dissertation was to evaluate the validity of skin conductance (SC) for pain assessment in hospitalized infants who were being mechanically ventilated. The age of infants in this dissertation ranges from the neonatal period (the first 28 days) to 12 months as defined by the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 2018). Preterm newborns were defined by the World Health Organization as babies born alive before 37 weeks of pregnancy are completed (World Health Organization, 2018). This introduction chapter orients the readers to: 1) pain in sick infants, 2) pain assessment in sick infants, 3) SC for pain assessment, 4) theoretical framework of validity testing, 5) knowledge gap, 6) the study purpose and objectives, and 7) an overview of the study methods.

Pain in sick infants

Before the 1980s, there was a widespread misbelief in the medical community that infants were not able to feel or express pain (Twycross, Dowden, & Bruce, 2009). The Jeffrey Lawson case in the United States of America (USA) and Dr. Kanwaljeet Anand's studies in England were the most seminal events to draw attention to pain in infants in the 1980s (McGrath, Stevens, Walker, & Zempsky, 2014). Jeffrey Lawson's mother described the case of her preterm infant's thoracotomy for patent ductus arteriosus ligation without anesthesia or analgesia, which was published in the Washington Post (Rovner, 1986). This story led to a change in attitude among the public and health care professionals (HCPs) about whether newborn babies could feel pain. Anand and colleagues conducted a series of studies

on pain in infants and demonstrated extensive adverse effects of surgery, such as respiratory, cardiovascular, metabolic and hormonal responses, and higher morbidity and mortality rates in neonates or infants who underwent surgery with no or minimal anesthetic or analgesic agents (Anand, 1990; Anand & Aynsley-Green, 1988; Anand, Brown, Bloom, & Aynsley-Green, 1985; Anand, Brown, Causon, et al., 1985; Anand & Hickey, 1987, 1992; Anand, Sippell, & Aynsley-Green, 1987; Anand, Sippell, Schofield, & Aynsley-Green, 1988). These studies, plus many more, illustrated that infants do experience pain, respond to pain and suffer adverse effects of pain.

Over the last three decades, knowledge of pain in infants has increased significantly (Chambers, 2018). A comprehensive bibliometric analysis of research articles on pediatric pain published from 1975 to 2010 illustrated a continued growth in the number of publications in the field of pediatric pain research since 1975 and revealed a notable increase since 1990 (Caes et al., 2016). Despite these advances, poorly treated infant pain is still acknowledged as a public health issue all over the world (Chambers, 2018).

The conceptualization of pain in infants

Due to the importance of the issue of pain, a global initiative was launched in 1995 to conceptualize pain as the fifth vital sign along with temperature, heart rate, blood pressure, and respiratory rate (American Pain Society, 1999; Frasco, Sprung, & Trentman, 2005). Although this initiative highlighted the importance of pain assessment, it also inherently placed pain in the context of the other four vital signs, which are objective, physiologically rooted, and easily and quickly obtainable in the clinical environment (Rollin, 1999).

However, pain is a subjective experience and complex phenomenon, which is much more difficult for HCPs to assess than the other four vital signs (Scher, Meador, Van Cleave, & Reid, 2018).

Two well-accepted definitions of pain were developed in the 1970s (International Association for the Study of Pain, 1979; McCaffery, 1972). First, McCaffery stated, “Pain is whatever the experiencing person says it is, existing wherever they say it does” (McCaffery, 1972). Second, the International Association for the Study of Pain (IASP) defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (International Association for the Study of Pain, 1979). The IASP pain definition has especially gained general acceptance and is used widely in the current scientific community (M. Cohen, Quintner, & van Rysewyk, 2018). These two definitions of pain illustrated that the experience of pain is both an individual and a subjective phenomenon and helped lay the foundation for self-report being the “gold-standard” of pain assessment (International Association for the Study of Pain, 1979; McCaffery, 1972). However, these two definitions fell short due to a lack of inclusion of non-communicating populations, including infants (Anand & Craig, 1996). This issue was addressed in 2001 when the following note was added to the IASP pain definition: “The inability to communicate in no way negates the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment” (International Association for the Study of Pain, 2001). Although this currently used IASP definition with the note is not flawless and is still under discussion by the scientific community (M. Cohen et al., 2018; Williams & Craig, 2016), it was used as the concept of pain in infants in this

dissertation.

Pain classification by duration of symptoms could include acute or nociceptive, subacute, ongoing acute, recurrent acute and chronic pain (American Society of Pain Management Nursing, 2010). Pain in this dissertation refers to acute pain, which is one of the most common adverse stressors experienced by infants (American Academy of Pediatrics & American pain society, 2001; Fitzgerald & Howard, 2003). It always occurs as a result of a specific nociceptive event, such as injury, skin-breaking procedures and tissue-damaging procedures, and is usually limited to a short period of time (McGrath et al., 2014).

Pain assessment is a process to evaluate different attributes of pain, such as intensity, onset, provoking, quality, region, timing, and impact. However, in this dissertation, pain assessment specifically refers to pain measurement, which is the assignment of a numerical value to quantify the intensity of pain (Finley & McGrath, 1998; Registered Nurses' Association of Ontario, 2013).

The terms “pain” and “stress” frequently interlink in the literature and are important to consider in infants. McIntosh et al. (1993) reflected that pain is always stressful; but stress is not necessarily painful (McIntosh, Van Veen, & Brameyer, 1993). However, infants’ lack of ability to report pain presents challenges distinguishing pain from stress (McIntosh et al., 1993). While most infant pain indicators are sensitive to painful events, they lack specificity to situations in which the infant is experiencing pain. Pain in infants is part of the wider phenomenon of stress, and stress may arise from many other facets of an infant’s hospitalization, which could be from non-painful procedures (e.g., handling or diaper change), hunger, or any other factors associated with the infant’s illness (Campbell, 1989).

Due to a lack of gold standard of pain measurement in infants, it is essential to consider infant pain responses as a dynamic interplay among biological, psychological, and social determinants of pain (Hadjistavropoulos & Craig, 2002). This idea was described by a few theories and models, such as the social communication model (Craig, 2009, 2015; Schiavenato & Craig, 2010), Fuller Infant Pain Assessment Model (Fuller, 1998) and the Onion Theory of Pain (Loeser & Melzack, 1999). These theories or models described the complex process of pain assessment and considered the biological, psychological, and social determinants and their effects on pain assessment (Craig, 2009, 2015; Fuller, 1998; Loeser & Melzack, 1999; Schiavenato & Craig, 2010). Guided by these theories or models, infant pain and its assessment needs to be considered along with the status of the individual infant before the painful event, the status of the individual infant's personal expression, the context of a dynamic, interactive process involving both the infant and caregiver and other pain-related contextual factors (Craig, 2009, 2015; Fuller, 1998; Loeser & Melzack, 1999; Schiavenato & Craig, 2010).

Prevalence of pain in sick infants

Critically ill infants need intensive medical attention and are admitted into neonatal intensive care units (NICUs) or pediatric intensive care units (PICUs). As NICUs and PICUs evolved, the number of new technologies for monitoring and lifesaving support has increased over the years (Boxwell, 2010). Emerging technologies have resulted in significant decreases in mortality and morbidity for critically ill infants (Boxwell, 2010). However, monitoring and therapy during intensive care are associated with repeated painful procedures and numerous

environmental stressors (Baarslag et al., 2018). Thus, infants in intensive care units can suffer pain, not only from their medical condition but also from painful procedures and other stressors including parental separation, constant noise and bright lights.

Sick infants during intensive care undergo large numbers of painful and distressing procedures as part of their routine care. A recent systematic review of the epidemiology of painful procedures illustrated that each sick infant underwent on average 7.5–17.3 painful and distressing procedures per day in the first 14 days of life or since admission in the hospital (Cruz, Fernandes, & Oliveira, 2016). This reported number of painful procedures is likely to be even lower than the real clinical situation, as the number of unsuccessful procedures was not always reported (Cruz et al., 2016). Painful procedures performed in infants have been categorized as skin-breaking procedures and traumatic or tissue-damaging procedures (Ahn & Jun, 2007). The most frequently performed skin-breaking procedures reported in the literature were heel lance and venipuncture, while airway suctioning and nasogastric tube insertion were reported as the two most frequent tissue-damaging procedures (Cruz et al., 2016).

In addition to repeated acute painful procedures, sick infants in NICUs and PICUs are subjected to numerous environmental stressors during their stay (Peng et al., 2009). NICUs and PICUs typically are illuminated 24 hours a day by a mixture of natural and artificial light. Constant light was reported as a contributing factor to physiological instability in infants, especially preterm infants (Ozawa, Sasaki, & Kanda, 2010). Excessive noise in intensive care units has also been a significant source of environmental stress for infants (Disher et al., 2017; Wachman & Lahav, 2011). The American Academy of Pediatrics recommended that

sound levels should not exceed 40-45 decibels in the NICUs or PICUs (American Academy of Pediatrics, 2002). However, the findings from a systematic review of 20 studies showed sound levels could easily reach 120 decibels on a regular and sometimes consistent basis in these studies (Casavant, Bernier, Andrews, & Bourgoin, 2017). The findings in other studies also showed that interventions minimizing sick infants' exposure to light and noise could significantly reduce infants' stress (Aita, Johnston, Goulet, Oberlander, & Snider, 2013; Casavant et al., 2017).

Mechanical ventilation was introduced in the 1960s as one of the significant new interventions in neonatology, especially for infants with respiratory failure (Donn & Sinha, 2003). It has become a common practice affecting a large proportion of the very low birth weight neonates as well as term newborn and older critically ill infants. The findings from one study showed that approximately 20 percent of all neonates in a NICU were intubated and mechanically ventilated (Zeller & Giebe, 2015). Research has demonstrated that mechanical ventilation constituted a significant nociceptive stimulus in sick infants (Hall, Boyle, & Young, 2007; Menon & McIntosh, 2008). Moreover, the sickest infants who require respiratory support by mechanical ventilation are more likely to receive a higher number of painful procedures compared to those not requiring mechanical ventilation (Cruz et al., 2016). One prospective observational study in a pediatric intensive care unit illustrated that mechanically ventilated pediatric patients underwent more than twice as many painful procedures than non-ventilated patients (Zhou et al., 2018). It was suggested that mechanically ventilated infants are at risk of being exposed to more stimuli and stressors during their intensive care compared to infants not requiring mechanical ventilation.

Despite significant advances in the knowledge of pain in infants, poorly managed pain in sick hospitalized infants is still acknowledged as a problematic issue for this population (McGrath et al., 2014). Cruz et al., (2016), in their systematic review, showed that the large majority (70%-90%) of painful procedures were performed without pain treatment (Cruz et al., 2016). They also demonstrated that pain treatment was less likely to be used in more vulnerable infants: those being mechanically ventilated; at high risk of neurologic impairment; less than 28 weeks of gestational age, and with higher severity of illness (Cruz et al., 2016). Thus, compared to other populations, neonates and infants requiring mechanical ventilation are at increased risk of experiencing moderate to severe acute pain during their hospital care (Groenewald, Rabbitts, Schroeder, & Harrison, 2012).

Adverse outcomes of pain in sick infants

In the first International Pain Summit on September 3, 2010, a document was developed which highlighted that access to pain management is a fundamental human right (International Association for Study of Pain, 2010). Early treatment of acute pain in sick infants during their intensive care is not only required for humanitarian and ethical reasons, but also because prolonged states of pain and poorly treated acute procedural pain may have significant short-term and long-term adverse physiological and psychological effects, potentially leading to disability and suffering later in life (McGrath et al., 2014).

Short-term effects of unmanaged acute pain include physiological compromise, including respiratory, cardiovascular, metabolic and hormonal adverse effects (Anand & Hickey, 1987; Twycross et al., 2009). Additionally, untreated pain may cause energy and

nutritional resources to be diverted away from growth and healing, resulting in decreased growth and development and reduced immune function (Twycross et al., 2009). Finally, poorly controlled pain in infants may impair their sleep and recovery, prolong their stay in hospitals, and ultimately, increase risk of death (Anand & Hickey, 1992).

Untreated pain in infants may also have long-term effects on their subsequent pain perception and responses, neurodevelopment, brain development and programming of stress systems (Hatfield, Meyers, & Messing, 2013; McGrath et al., 2014; Valeri, Holsti, & Linhares, 2015). Inadequate relief of pain and distress in full-term or preterm infants can stimulate their peripheral nociceptors and lead to long-term changes in the circuitry of the central nervous system, which may permanently decrease pain tolerance and increase pain responses later in life (Hatfield et al., 2013; McGrath et al., 2014). The altered structure and function of the nervous system and the sensitized subsequent pain perception may contribute to the development of chronic pain (Hatfield et al., 2013).

Compared to full-term infants, preterm infants are more susceptible to pain and long-term effects of pain, due to their immature but rapidly developing synaptic connections, integrated circuits, and descending endogenous modulatory controls (Fitzgerald & Walker, 2009; McGrath et al., 2014). A recent systematic review included 13 studies examining the association between early pain experiences of preterm infants and subsequent developmental outcomes (Valeri et al., 2015). The results showed statistically significant associations of neonatal pain experience with early and late developmental outcomes (Valeri et al., 2015). The developmental outcomes included postnatal growth, neurobehavior, cortical activation and brain development (Valeri et al., 2015). More specifically, unrelieved pain in preterm

infants was shown to lead to delayed postnatal body and head growth, reduced attention and arousal, lethargy, suboptimal reflexes, and structural brain abnormalities including reduced white matter, subcortical gray matter maturation, and reduced cortical thickness (Valeri et al., 2015). The number of painful procedures was the strongest predictor of poorer cognitive and motor development and altered temperaments, such as less mature ability to self-regulate and return to baseline functioning, poorer quality of focused attention, and high levels of internalizing behaviour in later life (Valeri et al., 2015). This highlights the need to ensure that painful procedures are minimized, and that effective pain management interventions are consistently used during painful procedures.

Pain assessment in sick infants

Pain assessment is an integral component of pain management in infants (Hall & Anand, 2014). Opioid analgesics are one of the most important pain treatments for mechanically ventilated infants (Tison, de Jonge, & Allegaert, 2009). However, opioid analgesics have a narrow therapeutic window (Zeller & Giebe, 2015; Zimmerman et al., 2017). Overdosing of opioid analgesics is associated with adverse effects, which include respiratory depression, sedation, hypotension, bradycardia, glottic and chest wall rigidity, urinary retention, ileus, and seizures (Taddio, 2002). Without a valid and reliable pain measurement, it is difficult for HCPs to tailor appropriate analgesia dosing for individual infants (Registered Nurses' Association of Ontario, 2013; Witt, Coynor, Edwards, & Bradshaw, 2016). Pain measurement has been stated as the foundation of scientific investigations in infant pain (Finley & McGrath, 1998). Pain measurement methods with valid and reliable scores enable researchers

to examine the nature, origins and correlates of pain in infants and to evaluate the effectiveness of interventions in clinical trials (Finley & McGrath, 1998). Thus, clinical practice and research studies of pain management in infants could benefit from utilizing accurate instruments to measure infant pain, potentially resulting in improved pain management, more appropriate treatments for infants and more reliable conclusions in research.

Tremendous advances have been made in understanding pain responses, and more than six dozen pain measurement tools have been developed for infants (McGrath et al., 2014). However, measuring pain in infants is still complex and challenging for researchers and HCPs (Cong, McGrath, Cusson, & Zhang, 2013; Hatfield & Ely, 2015; van Dijk & Tibboel, 2012). One of the critical challenges is lack of "gold standard" for measuring pain, as infants are unable to self-report pain (Pillai Riddell et al., 2016; Valitalo et al., 2016). Behavioural, physiological and multidimensional pain measurement methods are considered as surrogate approaches for self-report in infants (Cong et al., 2013; Lee & Stevens, 2014; Stevens, Riddell, Oberlander, & Gibbins, 2007; Stinson, 2009).

Physiological processes of acute pain in infants

The physiological processes of acute pain in infants are still not fully understood. However, a decade ago, Twycross et al. (2009) summarized what was known at the time about the pain pathways and physiological responses. For a stimulus to be perceived as pain, the noxious stimulus must be sufficiently intense to generate a nerve impulse, and the impulse must be transmitted via the many nerve pathways to the brain (Twycross et al.,

2009). The whole process is always described in four stages: transduction, transmission, modulation and responses (Twycross et al., 2009). Transduction is the process of nociceptors detecting a stimulus and generating a nerve impulse. Once a nerve impulse is generated, it is transmitted from the nociceptor to the spinal cord and then to the brainstem, hypothalamus, and thalamus (Twycross et al., 2009). The thalamus plays a role as the main relay station for sending the nerve impulse to different areas of the cerebral cortex for further processing (Almeida, Roizenblatt, & Tufik, 2004). Modulation is the process of exciting or inhibiting pain impulses. The descending pain pathway is primarily responsible for the modulation process. The pathway is originated from higher cortical areas (i.e., the amygdala and hypothalamus) and terminates in the spinal cord through the brainstem (Twycross et al., 2009). The process of the nerve impulse stimulating the central nervous system, such as the spinal cord, brainstem, thalamus, and cerebral cortex, contributes to the pain responses.

The underlying mechanism of the various pain assessment methods in infants is based on the pain responses from different areas in the nociception pathway (Fitzgerald & Walker, 2009). Biological markers, such as stress hormone levels, metabolic changes and inflammatory mediators, are not specific to one area, which is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (Biomarkers Definitions Working Group, 2001).” Except for biological markers, the other pain responses are reported to be specific to discrete areas in the central nervous system. When the nerve impulse from the stimulus reaches the spinal cord in infants, infants display clear nociceptive reflexive body movement, measurable as lower limb withdrawal and flexor muscle activity

(Fitzgerald, 2015). Facial expressions of pain, such as brow bulge, eye squeeze, naso-labial furrow, and open lips, are the reflexive facial reactions to noxious stimuli from the brainstem (Fitzgerald, 2015). When the nerve impulse processed in the spinal cord and brainstem is transmitted to the hypothalamus, the autonomic nervous system, including sympathetic and parasympathetic nervous systems, is stimulated to lead to the changes in vital signs and emotional sweating (Cowen, Stasiowska, Laycock, & Bantel, 2015). Measurement of cortical responses to pain in the cerebral cortex has been investigated by two approaches: hemodynamically (i.e., functional magnetic resonance imaging (fMRI), near-infrared spectroscopy (NIRS)) and biopotentials (i.e., electro-encephalography (EEG)) (Cowen et al., 2015; Verriotis, Chang, Fitzgerald, & Fabrizi, 2016).

Approaches to pain assessment in infants being mechanically ventilated

A multitude of pain assessment methods have been used to assess pain in mechanically ventilated infants. Such pain assessment methods can be classified as global pain measures, unidimensional single domain pain measures, unidimensional multiple domains pain measures, vital signs (i.e., heart rate, respiratory rate, oxygen saturation), multidimensional pain measures and other physiological indicators for pain assessment.

Global pain measures

The observational visual analog scale (VASobs) is an example of a global pain assessment measure. The approach of using visual analog scale (VAS) in older children and adults for estimating their global pain intensity is widely accepted. The VASobs has also been

used in infants, where pain was inferred on their behalf from the judgments of others (Buchholz, Karl, Pomietto, & Lynn, 1998; Taddio, Nulman, Koren, Stevens, & Koren, 1995; van Dijk, Koot, Saad, Tibboel, & Passchier, 2002). In the studies of infants requiring mechanical ventilation, the VASobs from the judgments of nurses or physicians was employed as the referent standard to validate other composite pain assessment scales such as the Premature Infant Pain Profile (PIPP), Neonatal Facial Coding System (NFCS), the Face, Legs, Activity, Cry and Consolability scale (FLACC), COMFORT scale and COMFORT behavioural scale (COMFORT-b) (Bai, Hsu, Tang, & van Dijk, 2012; Johansson & Kokinsky, 2009; Peters et al., 2003; Valitalo et al., 2016). The VASobs has also been used as an outcome measure in pain intervention studies in mechanically ventilated infants (Simons et al., 2003; van Dijk, Bouwmeester, et al., 2002). van Dijk et al., (2002) conducted a randomized controlled trial to evaluate the effects of continuous and intermittent morphine administration on pain responses (i.e. VASobs and COMFORT-b) in 180 infants aged up to three years old after major surgery (van Dijk, Bouwmeester, et al., 2002). Simons et al., (2003) conducted another randomized controlled trial to evaluate the effects of continuous morphine and placebo infusion on pain responses (i.e. VASobs, PIPP and Neonatal Infant Pain Scale) in 150 newborns who had received ventilatory support (Simons et al., 2003).

Foster (2001) suggested that the subjective judgments of HCPs should be the key factor in assessing pain in critically ill children (Foster, 2001), but this suggestion was based on the assumption that the observer is very familiar with the infant and also the situation being observed (Stevens, Johnston, & Gibbins, 2000). However, this assumption is not always met in clinical settings, and subjective judgments such as using the VASobs may be biased,

arising from the observers' personalities, the way they perceive the pain measurement in infants, or the contexts in which the observations are being conducted (Stevens et al., 2000). Thus, numerous studies have been conducted in this field to identify surrogate indicators of pain in infants with the aim of making judgments more objective and transparent (Walter-Nicolet, Calvel, Gazzo, Poisbeau, & Kuhn, 2017).

Unidimensional single domain pain measures

The NFCS is the most commonly used unidimensional single domain pain measure used in newborns (Grunau & Craig, 1987). It was adapted from the Facial Action Coding System (Ekman & Friesen, 1978) and is comprised of ten discrete facial actions (Grunau & Craig, 1987). It is considered as one of the most sensitive and specific measurements of acute procedural pain and forms the basis for most composite pain assessment tools for newborns and infants. The results in studies using NFCS in sick infants also showed that a subset of cluster of facial actions, comprised of brow bulge, eye squeeze, naso-labial furrow, and open lips was present most frequently in infants exposed to a painful stimulus (Grunau & Craig, 1987; Grunau, Johnston, & Craig, 1990; Grunau, Oberlander, Holsti, & Whitfield, 1998; Pereira et al., 1999). This four-item subset of the NFCS has been reported to produce reliable and valid scores for pain measurement in infants, and it has also been illustrated to be feasible for use at the bedside (Grunau et al., 1998; Harrison, Evans, Johnston, & Loughnan, 2002; Harrison, Johnston, & Loughnan, 2003; Rushforth & Levene, 1994).

The full NFCS or the subset of these four facial expressions is recommended as a measure of neonatal pain in many different guidelines (McGrath et al., 2014; Stevens et al.,

2007). It has been extensively evaluated in research studies and used as an outcome measure for intervention studies. For example, a prospective observational study was conducted to evaluate the validity of the NFCS for assessing postoperative pain in 37 children (0–18 months old) undergoing major abdominal or thoracic surgery (Peters et al., 2003). The 37 children included 11 neonates up to four weeks old, 17 four-week to six-month old children and nine six- to eighteen-month old children, of which nineteen were mechanically ventilated in the postoperative period (Peters et al., 2003). However, the overall number of infants undergoing mechanical ventilation was not specified (Peters et al., 2003). Peters et al., (2003) found statistically significant positive associations of NFCS scores with other pain measurements, including bedside nurses' VASobs, COMFORT-b and physiological parameters (heart rate and heart rate variability and blood pressure). In addition, findings showed that five of the original ten facial expression scores were substantially interrelated and could be combined into a reduced measure of pain (Peters et al., 2003). These five interrelated NFCS items were brow bulge, eye squeeze, naso-labial furrow, horizontal mouth stretch, and taut tongue (Peters et al., 2003). The five-item NFCS subset was also statistically positively associated with all the other pain measurements (Peters et al., 2003). Peters and colleagues suggested that reducing the ten-item NFCS to five items appears to increase the feasibility and clinical utility of this scale without reducing the validity of pain assessment in mechanically ventilated infants (Peters et al., 2003). Besides the validation study, the NFCS has been used as an outcome measure in three clinical trials which have included mechanically ventilated infants (Alencar et al., 2012; Boyle, Freer, Wong, McIntosh, & Anand, 2006; Taddio et al., 2006). Alencar et al., (2012) used the NFCS with all the ten items

to evaluate the efficacy of tramadol versus fentanyl for postoperative pain in 160 neonates, who were up to 28 days of life requiring major and minor surgeries, in a controlled, blind, randomized clinical trial (Alencar et al., 2012). Boyle et al., (2006) and Taddio et al., (2006) only used one of the facial actions (i.e., brow bulge) as a pain outcome to evaluate the effectivenes of morphone versus placebo for persistent pain in ventilated preterm infants in NICUs and the effectiveness of morhphine versus topical tetracaine for acute pain in ventilated preterm infants undergoing central line placement (Boyle et al., 2006; Taddio et al., 2006).

Unidimensional multiple domains pain measures

The COMFORT-b and FLACC are unidimensional pain measures, as they only include behaviour indicators, involving two different domains: facial actions and nociceptive reflexive body movements. The COMFORT-b was adapted from the COMFORT pain assessment scale, which was initially developed to assess pain or distress in critically ill pediatric patients from birth to 18 years (Ambuel, Hamlett, Marx, & Blumer, 1992). Following revision of the COMFORT, the two physiological indicators of blood pressure and heart rate were removed, while keeping the six behavioural items of alertness, calmness and agitation, physical movement, muscle tone, facial tension, and respiratory response in mechanically ventilated infants and children or crying in spontaneously breathing children. The reason of keeping the six behavioural items was that these items explained most of the variance in pain scores and were shown to be more specific to pain than the physiological measures (Ambuel et al., 1992; Maaskant et al., 2016). The FLACC is comprised of five

behaviours, including face, leg, activity, cry, and consolability (Crellin, Harrison, Santamaria, & Babl, 2015; Merkel, Voepel-Lewis, Shayevitz, & Malviya, 1997).

The COMFORT-b and FLACC scores were assessed for validity against the VASobs for measuring postoperative pain in two observational studies which included mechanically ventilated infants and children (Bai et al., 2012; Johansson & Kokinsky, 2009). In the study by Johansson and Kokinsky (2009), the COMFORT-b, FLACC and VASobs were measured in 40 children aged birth to 10 years, randomly on two to three different occasions (e.g., after cares, before and after analgesics) in the first 24 hour post-operative period (Johansson & Kokinsky, 2009). The results showed that the COMFORT-b and FLACC both had statistically significantly moderate and positive correlations with the VASobs (Johansson & Kokinsky, 2009). In the study by Bai and colleagues (2012), the COMFORT-b, FLACC and VASobs were measured in 170 children aged birth to seven years, at two-hour intervals on the day of surgery and the first 48 hours postoperatively (Bai et al., 2012). The results showed that the COMFORT-b had a weak but statistically significantly positive correlation with the VASobs, and the FLACC had a statistically significantly positive and strong correlation with the VASobs. The validity of FLACC alone was also evaluated in another observational study of 35 mechanically ventilated children between 1 month and 12 years of age (Dantas, Dantas, Santana Filho, Azevedo-Santos, & DeSantana, 2016). The results showed the FLACC scores during arterial blood collection for blood gas analysis were statistically significantly higher than those immediately before and five minutes after the procedure (Dantas et al., 2016).

In addition, the COMFORT-b was used as a pain outcome measure in one randomized

controlled trail, testing the efficacy of continuous versus intermittent morphine administration after major surgery in mechanically ventilated infants and children (van Dijk, Bouwmeester, et al., 2002). In one retrospective study describing the effectiveness of continuous infusion hydromorphone in mechanically ventilated infants and children, the FLACC was used as a pain outcome measure in the units at a tertiary care pediatric hospital (Reiter, Ng, & Dobyns, 2012). However, these studies assessing the validity of scores obtained with or using the COMFORT-b or FLACC not only included infants (newborns to one year old), but also involved older children (up to less than 18 years old) (Bai et al., 2012; Dantas et al., 2016; Johansson & Kokinsky, 2009; Reiter et al., 2012; van Dijk, Bouwmeester, et al., 2002). As the results of infants and older children requiring mechanical ventilation were not reported separately in all the studies, it is difficult to conclude that the scores of the COMFORT-b or FLACC showed good validity for pain assessment in mechanically ventilated infants specifically.

Although the behavioural indicators of facial expression or nociceptive reflexive body movement are widely used as part of most pain assessment scales to assess pain in hospitalized infants, there are significant limitations when using these indicators in infants who are mechanically ventilated. The airway tube, tube holder, and *tape* over an infant's face may limit clinicians' view and accurate assessment of the infant's facial expressions (Arif-Rahu & Grap, 2010). It is difficult to assess the nociceptive reflexive body movements, as critically ill infants, especially neonates, may be restrained to avoid accidental removal of medical devices, swaddled, or they may lack sufficient energy to demonstrate body movements (Anand, Stevens, & McGrath, 2007). Neuromuscular blockers or deep sedation

may also be used in clinical settings to reduce critically ill infants' resistance to mechanical ventilation, if needed. These medications preclude facial expressions or nociceptive reflexive body movements (Herr, Coyne, McCaffery, Manworren, & Merkel, 2011).

Vital signs

Changes in vital signs such as heart rate, blood pressure, respiratory rate, and oxygen saturation are responses of the autonomic nervous system to pain and are easily observed through bedside cardio-respiratory and oxygen saturation monitors (Cowen et al., 2015). Although the validity of vital signs has not been specifically tested in response to pain in mechanically ventilated infants, it was used in three trials as a single outcome measure of pain evaluating pain treatment in this population (Alencar et al., 2012; Franck et al., 2000; Saarenmaa, Huttunen, Leppaluoto, Meretoja, & Fellman, 1999). Heart rate, respiratory rate and oxygen saturation were monitored in Alencar et al., (2012) study; Vagal tone index, which is the pattern of heart rate variability occurring within the frequency range of the neonate's respiratory rate, was evaluated in Franck et al., (2000) study; heart rate, arterial blood pressure and oxygen saturation were monitored in Saarenmaa et al., (1999) study.

The use of heart rate in response to pain is pervasive in the hospital setting. However, a recent systematic review demonstrated that research evaluating cardiovascular indices of response (i.e., mean heart rate, heart rate change or heart rate variability) to acute pain in infants is still inconsistent (Waxman, Pillai Riddell, Tablon, Schmidt, & Pinhasov, 2016). In addition, many clinical practice guidelines recommend that HCPs should minimize emphasis on heart rate, blood pressure, respiratory rate and oxygen saturation for pain assessment, as

vital signs are affected by many factors other than pain, such as pulmonary and cardiovascular diseases, mechanical ventilation, cardioactive and vasoactive drugs, or circulatory changes (Barr et al., 2013; Herr et al., 2011; Registered Nurses' Association of Ontario, 2013).

Evidence that supports using vital signs as a single indicator of pain is limited; however, in combination with facial expressions, nociceptive reflexive body movement and/or contextual indicators of pain, changes in vital signs from baseline states may add crucial additional information from a different dimension regarding infant response to acute pain (Stevens et al., 2000). It is suggested that a comprehensive assessment from multiple dimensions may be warranted due to the complex nature of pain (Stevens et al., 2007).

Multidimensional pain measures

Both the PIPP and COMFORT are multidimensional pain measures combining multiple items from multiple dimensions. The PIPP includes three behavioural responses (facial actions of brow bulge, eye squeeze, and naso-labial furrow), two physiological responses (heart rate and oxygen saturation), and two contextual items (gestational age and behavioural state) (Stevens, Johnston, Petryshen, & Taddio, 1996). The validity of PIPP has been extensively evaluated for the assessment of pain in both preterm and term infants, is commonly recommended in pain assessment guidelines and is widely used in clinical settings (Stevens, Johnston, Taddio, Gibbins, & Yamada, 2010). The PIPP is also the most frequently used pain measurement for evaluating pain outcomes in interventional studies testing different pain treatments (e.g., fentanyl, remifentanil, morphine, melatonin) in mechanically

ventilated infants (Anand et al., 1999; Ancora et al., 2013; Cignacco et al., 2008; Gitto et al., 2012; Hartley et al., 2018; Qiu et al., 2018; Shin et al., 2014; Simons et al., 2003; Valitalo et al., 2017).

In 2014, on the basis of a comprehensive review of the psychometric properties of PIPP for measurement of pain in infants, and feedback from researchers and clinicians, the PIPP was revised to the Premature Infant Pain Profile-Revised (PIPP-R) to address validity and feasibility concerns in all gestational age groups and behavioural states (Gibbins et al., 2014; Stevens et al., 2014). The PIPP-R has the same indicators but a different scoring system from the original version (Stevens et al., 2014). Each item is numerically scaled and scored on a 4-point scale (0 to 3 points) reflecting changes in each variable from baseline values. The scores obtained for the 7 items are summed for a total pain intensity score, ranging from 0 to 21; however, the two contextual items are scored only if subtotal score for the physiological and facial indicators is greater than zero.

The PIPP and COMFORT have been evaluated together in one validation study involving infants requiring mechanical ventilation (Valitalo et al., 2016). The study built an item response theory model for detecting pain as the latent variable in 118 mechanically ventilated neonates undergoing endotracheal and nasal suctioning, using items from these two scales (Valitalo et al., 2016). The results showed that the scores of the behavioural items of the PIPP and COMFORT were superior to physiological items based on their informativeness in quantifying pain in mechanically ventilated neonates during painful stimuli (Valitalo et al., 2016). As a result, Valitalo et al. (2016) suggested that the use of physiological items in pain research and assessment of pain in clinical practice should be discouraged (Valitalo et al.,

2016). This suggestion is in accordance with previous critics that mixing poorly correlated dimensions in total scores is not justified and may lead to inaccurate pain assessment with potential for subsequent ineffective pain management (McDowell, 2006; McGrath et al., 2014).

Physiological indicators for pain assessment

In addition to the more commonly used physiological parameters of heart rate, blood pressure, respiratory rate, and oxygen saturation, other physiological indicators for pain assessment include biological markers, cortical indicators and changes in the sympathetic nervous system, such as SC. Biological markers for pain assessment are mostly used in research, rather than for routine clinical assessment (Cowen et al., 2015). One of the reasons could be that biomarkers used in pain assessment, such as cortisol, leukocyte count, C reactive protein, and catecholamines reflect responses to inflammation or tissue damage rather than pain (Marchi, Vellucci, Mameli, Rita Piredda, & Finco, 2009). In addition, biological markers are most often measured by blood work, which causes additional pain to infants and is not feasible, nor ethical for HCPs to measure and assess infant pain in real time (Registered Nurses' Association of Ontario, 2013).

There is growing interest in the role of the cerebral cortex in pain neurophysiology and transmission of noxious stimuli from the nociceptors to the central nervous system (Fitzgerald, 2015). The majority of studies have been conducted in animals (McGrath et al., 2014); however, a recent systematic review synthesized the evidence of neurophysiological methods used in infant acute pain assessment (Benoit, Martin-Misener, Newman, Latimer, &

Campbell-Yeo, 2017). In this review, nine studies were identified using the NIRS, eight studies using EEG, and two studies using fMRI (Benoit et al., 2017). The results of the systematic review showed great variability of methodologies used in the studies and found that there was no definitive conclusion in the usefulness of these novel non-invasive cortical indicators for pain assessment (Benoit et al., 2017). Thus, pain measurement using cortical indicators is an emerging area of research but is far from being applicable in clinical settings (McGrath et al., 2014).

The use of SC for assessing pain has been studied in more than 70 studies in populations across the life span (Ledowski, Albus, Stein, & Macdonald, 2011; Lyngstad, Tandberg, Storm, Ekeberg, & Moen, 2014; Strehle & Gray, 2013). Only one study has tested the validity of SC in response to procedural pain in mechanically ventilated infants (Karpe, Misiolek, Daszkiewicz, & Misiolek, 2013). The study included 32 mechanically ventilated neonates born between 34 and 39 weeks gestation. The results showed that the SC value was significantly higher during airway suctioning or blood sampling than at rest (Karpe et al., 2013). The authors suggested that SC holds promise as a physiological indicator to be used in research or clinical practice to advance our understanding of pain and stress responses in mechanically ventilated infants. SC is the measurement of emotional sweating, which is one of the responses activated by the autonomic nervous system. While heart rate, respiratory rate, and oxygen saturation are controlled by the sympathetic nervous system and parasympathetic nervous system, SC is only controlled by the sympathetic nervous system (Cowen et al., 2015). The sympathetic nervous system is catabolic and activates fight-or-flight responses, and the parasympathetic nervous system is anabolic and mediates

homeostasis (Walker, Hall, & Hurst, 1990). Thus, SC is specifically related to stress, whereas heart rate, respiratory rate and oxygen saturation are related to needs of internal viscera (homeostasis) and external challenges (stress) (Stevens et al., 2007).

Skin conductance for pain assessment

SC is a measurement of electrodermal activity. Since the 1840s, when electrodermal phenomena, or emotional sweating, was first observed, electrodermal activity recording has become one of the most commonly used bio-signals in both basic science and clinical research (Boucsein, 2012). One of the reasons for the popularity of electrodermal activity recordings is the ease of obtaining the values of a distinct electrodermal activity in laboratory and field conditions (Kucera, Goldenberg, & Kurca, 2004). The history of the measurement of skin conductance, the physiological process of skin conductance, and the Med-Storm skin conductance device for pain assessment in infants are introduced in this section.

History of the measurement of skin conductance

The early history of research into electrodermal activity was reviewed by Neumann and Blanton (1970), although specific details of many of the studies are missing. The experiment which first observed electrodermal activity dates back to 1849 and was conducted by Dr. DuBois-Reymond in Germany (Neumann & Blanton, 1970). DuBois-Reymond had the participants in his study put their feet into a zinc sulfate solution and observed an electrical current going from one limb to the other (Neumann & Blanton, 1970). The study which first related electrodermal activity to a stimuli could be attributed to Dr. Vigouroux (1879), an

electrotherapist working in France (Neumann & Blanton, 1970). He measured electrodermal activity changes that paralleled changes in the amount of anesthesia when patients who were diagnosed with hysteria, received treatments (Neumann & Blanton, 1970).

Electrodermal activity was first introduced by Johnson and Lubin (1966) as a collective term for all electrical phenomena in the skin, including all active and passive electrical properties which can be traced back to the skin and its appendages (Johnson & Lubin, 1966). One year later, a proposal for term standardization made by a terminology commission of the Society of Psychophysiological Research had been published (Brown, 1967). The term electrodermal activity and its related terms are now generally accepted (Boucsein, 2012). The use of SC is related to stimulus intensity or psychological significance and provides a more standardized method of measurement compared to skin resistance, as skin resistance varies with the state of sweat glands in the skin (Lykken & Venables, 1971; Montagu & Coles, 1966).

More recently, SC has been widely used in the fields of psychology for measuring attention and arousal (Prokasy & Raskin, 1973), criminology for detecting deception (Meijer, Verschuere, Gamer, Merckelbach, & Ben-Shakhar, 2016), and neurology for testing the function of the sympathetic nervous system (Novak, 2017). SC was first introduced in the hospital setting for pain assessment in patients undergoing elective surgery and general anesthesia in 1982 (Goddard, 1982). Goddard (1982) monitored SC changes in 67 patients as part of a pilot study involving two groups of patients undergoing general anesthesia and surgery (Goddard, 1982). The findings of the study were that SC changes were present in response to surgical stimulus in the group receiving nitrous oxide and oxygen but not present

in the group receiving the general inhalation anesthetic, halothane (Goddard, 1982). However, the study methods were not reported in detail, including the group allocation methods, type of surgery, and type of surgical stimulus (Goddard, 1982).

Physiological process of skin conductance

The measurement of SC is a physiological approach to measuring pain which is based on emotional sweating (Gladman & Chiswick, 1990; Harpin & Rutter, 1982). Sweat glands produce and absorb sweat (Sato & Dobson, 1970). They are found all over the body but are most common in palms of hands and soles of feet (Sato & Dobson, 1970). There are approximately 400 sweat glands to be found within one square millimeter of the palmar and plantar regions (Sato & Dobson, 1970).

Each time the sympathetic nervous system is activated, the nerve endings that originate from the paravertebral chain of sympathetic ganglia release acetylcholine (Wilkins, Chung, Tublitz, Wong, & Minson, 2004). The released acetylcholine acts on the M3 muscarinic acetylcholine receptors on sweat glands (Wilkins et al., 2004). Consequently, sweat is released by sweat glands in palms of hands and soles of feet within 1-2 seconds and fills up sweat gland ducts immediately (Wilkins et al., 2004). This process leads to increases in SC (Wilkins et al., 2004). When the sympathetic nervous system stops sending impulses, sweat is reabsorbed quickly and SC decreases (Wilkins et al., 2004).

Sweating in the palms of hands and soles of feet is also influenced by high ambient or central temperature, which is known as thermal sweating (Bini, Hagbarth, Hynninen, & Wallin, 1980). However, thermal sweating has different characteristics from emotional

sweating. Thermal sweating is activated by the hypothalamus which receives the sensory information of high ambient or central temperature (Bini et al., 1980). Thermal sweating is a gradual process with small amplitudes as measured by SC. However, emotional sweating has prominent amplitudes and no latent period before the onset and also subsides rapidly once the stimulation ends (Storm, 2008).

Since SC reflects the activation of the sympathetic nervous system, it is influenced by factors that influence the sympathetic nervous system. These factors include extreme prematurity, less than 25 weeks gestation (immature sympathetic nervous system); injury to the skin where the SC probes need to be placed (lack of sweat glands); an implanted defibrillator or pacemaker (electricity disorder); high dose atropine and neostigmine (cholinergic activating or blocking drugs to inhibit or enhance transmission of acetylcholine); and clonidine (sympathetic inhibitors) (Schlereth & Birklein, 2008; Storm, 2008, 2013). As neuromuscular blockers, adrenergic receptor active agents and cardioactive or vasoactive drugs do not act on M3 muscarinic acetylcholine receptors, these agents used in mechanically ventilated infants are not expected to influence SC (Schlereth & Birklein, 2008; Storm, 2008, 2013).

Med-Storm skin conductance device for pain assessment in infants

The Med-Storm SC monitoring device, including the apparatus and software program, was commercially developed by Med-Storm Innovations (Figure 1-1) (Med-Storm Innovation AS, 2012; Storm, 2001a). The Med-Storm device has not been used in clinical practice, but it is the most commonly used SC measurement device in research (Choo, 2013;

Storm, 2008, 2013). It measures the electrodermal activity between the electrodes placed on the plantar or palmar area which are rich with sweat glands (Vetrugno, Liguori, Cortelli, & Montagna, 2003). According to the Med-Storm device manual, it is recommended that the electrodes should be best placed on one of the infant's feet to capture SC in the plantar region (Med-Storm Innovation AS, 2012). The three-electrode system of the apparatus comprises a measuring electrode (black) placed on the sole, a counter current electrode (yellow) placed on either side of the ankle, and a reference voltage electrode (blue) placed on the other side of the ankle (Figures 1-2, 1-3).

The Med-Storm device is non-invasive, portable and automated (Med-Storm Innovation AS, 2012). SC activity is measured by the amount of current passing at a constant voltage between the electrodes (Hagbarth, Hallin, Hongell, Torebjork, & Wallin, 1972). With filling and absorption of sweat in the sweat glands, the SC device monitors the increasing and decreasing electrodermal activity, records SC activity peaks and troughs on the screen, and calculates the values of different SC parameters (Figure 1-4) (Med-Storm Innovation AS, 2012).

SC parameters include mean SC level, number of waves per second (NWps), average peak, rise time, area under curve, area huge peaks, and area small peaks. Mean SC level is the average value of SC activities in a time window (Med-Storm Innovation AS, 2012). The NWps, which is sometimes referred to as number of peaks per second in literature, is the number of waves in the window divided by the time span of the window (Med-Storm Innovation AS, 2012). The peak value is the difference in SC level between the identified maximum and minimum of one peak (Med-Storm Innovation AS, 2012). Average peak is

calculated from all peaks in the time window (Med-Storm Innovation AS, 2012). Rise time is the time window of SC level increasing from the minimum point of one peak to the maximum (Med-Storm Innovation AS, 2012). The parameter “area huge peaks” is the accumulated area between the SC levels at the maximum point of one peak and the minimum (Med-Storm Innovation AS, 2012). The parameter “area small peaks” is the accumulated area between the SC levels at the two adjacent minimum points of one peak (Med-Storm Innovation AS, 2012). Area under curve is the same to bigger values of either the parameter “area huge peaks” or “area small peaks” (Med-Storm Innovation AS, 2012).

Recommended by previous research and also the Med-Storm device manual, the fifteen seconds time span is the best time window to calculate SC values (Ledowski et al., 2011; Med-Storm Innovation AS, 2012; Storm, 2009, 2011). Higher values in any of the above SC parameters are indicative of higher activation of the skin sympathetic nerves, which could be caused by stress or pain. Among these SC parameters, the NWps has been demonstrated to be the most accurate SC parameter for pain assessment (Macko, Moravcikova, Kantor, Kotikova, & Humpolicek, 2014; Storm, 2008, 2013; Valkenburg, Niehof, van Dijk, Verhaar, & Tibboel, 2012).

Theoretical framework of validity testing

The purpose of measurement is to assign a value to a concept (Nunnally & Bernstein, 1994). Therefore, the purpose of the infant pain measurement is to assign a value to pain intensity for a particular infant at a particular time (Finley & McGrath, 1998). The Assessment and Management of Pain Clinical Best Practice Guideline developed by the

Registered Nurses' Association of Ontario (RNAO) (2013), recommended that pain assessment tools need to be consistent and result in trustworthy ratings, regardless of time, setting or who is administering the measure; truly measure the intended type of pain it was created to measure; be able to detect change in pain due to the implemented pain management interventions; be simple and quick to use, and be appropriate and practical to clinical settings (Registered Nurses' Association of Ontario, 2013). The RNAO also suggested the pain assessment tools should be developmentally and culturally appropriate for the population it is designed for, available in various languages or easily translatable, easily and quickly understood by the person, liked by persons, clinicians and researchers using it, and able to be disinfected if touched by a person (Registered Nurses' Association of Ontario, 2013).

Among these 11 recommended criteria, validity testing is the most important step in introducing a pain assessment tool to the clinical setting, as random and systematic measurement errors can impede accurate pain measurement (Finley & McGrath, 1998; Waltz, 2016). Despite the centrality of validity to scientific measurement, there is no consensus on the explanation of validity and the process of validity testing among theorists (Raykov, 2011). According to different views and perceptions on validity and validity testing, various standards, guidelines or frameworks in different disciplines regarding the development or evaluation of measurement instruments have been developed. These include American Educational Research Association (AERA) Standards for Psychological Testing, Guidance for Industry-Patient-Reported Outcomes Measures, Consensus-Based Standards for the Selection of Health Measurement Instruments, Evaluating the Measurement of Patient-

Reported Outcomes, Principles for the Validation and Use of Personnel Selection Procedures (American Educational Research Association, 2014; Chan, 2014; L. L. Cohen et al., 2008; Stevens et al., 2010).

American Educational Research Association Standards for Psychological Testing

The AERA Standards were applied in this dissertation as a theoretical framework for examining the validity evidence of SC for pain assessment in infants (American Educational Research Association, 2014). The concept of validity in the AERA Standards is heavily influenced by Messick's unitary view of validity (American Educational Research Association, 2014; Messick, 1995). In his view, construct validity is the central component in validation work and encompasses the sources of evidence germane to the validation of the interpretation and use of the score of an instrument (Messick, 1995). This idea leads to the view that validity is no longer a property of the measurement but describes the range of interpretations that can be appropriately placed on a measurement score some person produced in some setting (American Educational Research Association, 2014). The approach is in accordance with the concept of pain, which is an abstract variable strongly influenced by pain stimulus, clinical context, and the characteristics of the individual (McDowell, 2006). The other viewpoint is that the AERA Standards not only consider the findings obtained from traditional observational studies, which specifically aim for validating the targeted instrument as validity evidence, but also include the findings from interventional studies, which use the targeted instrument as the outcomes. Last, the AERA Standards are considered the best practice in the field of psychometrics and have also been commonly used in the field of

health sciences (Squires et al., 2015; Streiner, 2008).

The AERA Standards illustrated that four sources of validity evidence needed to be collected and analyzed: content, response processes, internal structure, and relation to other variables (American Educational Research Association, 2014). Validity evidence as it relates to content aims to test the relationship between the items, format and wording of the items in an instrument and the concept it intends to measure (American Educational Research Association, 2014). Validity evidence in response processes refers to the examination of the cognitive or thinking processes involved when people respond to items (American Educational Research Association, 2014). Validity evidence relating to internal structure refers to the degree to which the items represent the construct of interest by investigating how items relate to each other using statistical methods such as factor analysis and item response modeling (American Educational Research Association, 2014). Validity evidence in relation to other variables concerns the association of the scores of the tested instrument with the scores of other variables (American Educational Research Association, 2014). As the SC device is a physiological monitor, the objective measurement makes validity evidence of SC in content and response processes redundant. It is also unnecessary to test validity evidence based on internal structure, as SC is a unidimensional measurement. In this dissertation, the validity of SC for pain assessment in infants was tested using the evidence in relation to other variables, for example, referent pain measures, type of stimuli, infant age, and other contextual factors.

Knowledge gap

There have been numerous studies on SC for pain assessment in all populations throughout the age spectrum, from neonates to adults. Three narrative reviews on the validity evidence of SC have been published (Choo, 2013; Storm, 2008, 2013). The first review concerned the benefits and challenges of using Med-Storm SC monitoring device in research and clinical practice (Storm, 2008). The second review published five years later aimed to synthesize the evidence on the clinical use of SC for monitoring postoperative pain assessment (Choo, 2013). In this review (Choo, 2013), six studies were included and involved four studies with 244 adults (Czaplik et al., 2012; Ledowski et al., 2006; Ledowski, Bromilow, et al., 2007; Ledowski, Preuss, & Schug, 2009) and two studies with 255 children older than seven years (Choo et al., 2010; Hullett et al., 2009). The correlations of SC for assessing pain compared with self-report pain scales (i.e. numerical rating scale and VAS) in these studies were evaluated. The results showed SC had positive correlations with self-report pain scales (correlation coefficient=0.165-0.625), with three studies demonstrating statistically significant findings (Hullett et al., 2009; Ledowski et al., 2006; Ledowski, Bromilow, et al., 2007) but the other three studies demonstrating statistically non-significant findings (Choo et al., 2010; Czaplik et al., 2012; Ledowski, Ang, Schmarbeck, & Rhodes, 2009). This review (Choo, 2013) stated that one of the possible reasons for the variability in results was the various methods used across the studies, which included inconsistent observation time intervals of the NWps, different cut-off values for the NWps for different levels of pain, and use of different statistical methods. The third review, which was also published in 2013, compared SC for assessing pain in children with other physiological pain

assessment methods, including heart rate, blood pressure, oxygen saturation and the NIRS (Storm, 2013). The authors of this review suggested that SC is more accurate for pain assessment in children than the other physiological pain assessment methods. However, only PubMed was searched, and the results were only narratively described. Thus, none of the three reviews systematically synthesized the knowledge on the validity of SC for assessing acute pain in infants. It is therefore important to systematically synthesize the validity evidence of SC for assessing acute pain in infants, including the methods of research conducted in this field.

Most studies which evaluated or used SC for pain assessment in infants included healthy newborns or medically stable hospitalized infants, who were not receiving mechanical ventilation. As mentioned previously in the section "physiological indicators for pain assessment", there is only one study reporting SC for pain assessment in mechanically ventilated infants (Karpe et al., 2013). However, critical limitations to Karpe's study include a lack of comparison of SC with any referent pain measures and a lack of comparison of SC values during painful procedures to non-painful procedures. Without these comparisons, it is difficult to tell whether the higher SC values during painful procedrues compared to baseline and recovery were induced by pain. In addition, the methods section was reported in insufficient detail to enable replication of the study (Karpe et al., 2013). As SC changes continuously during the measurement, it is essential to report the method (i.e., maximum, minimum or average value) and the observation time interval (e.g., 10 seconds, 20 seconds and 30 seconds) of sampling SC values before, during and after procedures. Lastly, the NWps is the number of peaks in the time window divided by the time span of the window (Med-

Storm Innovation AS, 2012). For the same SC level, the NWps may differ when the time window is different (Ledowski et al., 2011). Thus, it is also important to report the time span of the windoe (e.g., 10 seconds, 20 seconds and 30 seconds). Therefore, further research is needed before SC for pain assessment can be recommended as applicable in the clinical settings, especially in critically ill infants requiring mechanical ventilation.

Purpose and objectives

This overall purpose of the dissertation was to evaluate whether SC is a promising method of pain measurement in critically ill infants, who require painful procedures as part of their medical care. This dissertation will contribute to advancing knowledge on pain measurement in this vulnerable infant population. This dissertation comprises two studies (i.e., one scoping review and one primary study), which are reported in two manuscripts.

The purpose of the first study was to conduct a scoping review to identify the extent of research conducted and to synthesize the validity evidence of SC for assessing acute pain in infants. Specifically, the objective of this scoping review was to address the research question of "what is the validity evidence of SC for assessing acute pain in infants in the literature and how have the validation studies been done."

The purpose of the second study was to evaluate the validity of SC for pain measurement in mechanically ventilated infants in relation to: 1) the type of procedure (painful compared to non-painful); 2) the phase of procedure (before, during and after procedure), and 3) referent pain measures (i.e., PIPP-R and the four-item NFCS), which are widely used in research and clinical practice. Specifically, this study tested the following four

hypotheses:

1. Infants being mechanically ventilated have statistically significantly different NWps during painful procedures compared to non-painful procedures.
2. Infants being mechanically ventilated have statistically significantly different NWps during painful procedures compared to before or after painful procedures.
3. There is no difference in NWps in infants being mechanically ventilated between during non-painful procedures and before or after non-painful procedures.
4. The NWps of infants being mechanically ventilated has statistically significant correlations with PIPP-R and the four-item NFCS before, during and after procedures.

Methods overview

Study One: The Validity of Skin Conductance for Assessing Acute Pain in Infants: A Scoping Review

A scoping review is a form of knowledge synthesis that addresses an exploratory research question and aims at mapping key concepts, types of evidence, and gaps in research related to a defined area or field (Colquhoun et al., 2014). A scoping review is carried out to determine not only the extent of the research available regarding a topic but also the way the research has been conducted (The Joanna Briggs Institute, 2015a). In 2005, Arksey and O'Malley offered a five-stage methodology framework for conducting scoping reviews (Arksey & O'Malley, 2005). This framework has been influential in the conduct of scoping reviews (Tricco et al., 2016). In subsequent work, Levac et al. (2010) and Daudt et al. (2013)

provided more explicit details regarding what occurs at each stage of the review process which has increased both the clarity and rigor of the scoping review methodology. Arksey and O'Malley's framework incorporating the subsequent advanced recommendations (Arksey & O'Malley, 2005; Daudt, van Mossel, & Scott, 2013; Levac, Colquhoun, & O'Brien, 2010) was used to inform the scoping review of the validity evidence of SC for assessing acute pain in infants. Detailed description of Study One methods has been provided in Manuscript One.

Study Two: The Validity of Skin Conductance for Measuring Pain in Mechanically Ventilated Infants

A prospective cross-sectional observational design was used to study SC and its relation to other pain measures in mechanically ventilated infants before, during and after a painful and non-painful procedure. This study was approved by the CHEO Research Ethics Board (17/85X) and University of Ottawa Research Ethics Board (A08-17-06) (Appendix A). This study was funded by the Sigma Theta Tau International/Rosemary Berkel Crisp Research Award (2018-2019) and Canadian Pain Society Trainee Research Award (Clinical Science, 2018-2019); none of which had a role in study design, data collection and analysis, publication decisions, or preparation of the manuscripts or dissertation (Appendix B). Although Study Two methods were described in Manuscript Two, some details on patient recruitment, adverse event reporting, data collection procedure, data management, and participants' withdrawal, are not provided due to the word count limit of the journal. In this following section, these details are provided.

Patient recruitment

Participating infants were recruited from the NICU and PICU at the Children's Hospital of Eastern Ontario (CHEO). Recruitment posters for parents were posted in the area for family rest and on the unit research whiteboard that parents can access (Appendix C). Recruitment posters for staff were posted in each nursing station, staff office and the staff room (Appendix D). Eligible infants were identified daily by bedside nurses in the circle of care or care facilitators in charge of the shift. If potentially eligible according to the inclusion and exclusion criteria (Appendix E, F), the investigator (the Ph.D. candidate or one research assistant) asked bedside nurses or care facilitators if they could approach the parents/guardians to check whether the parents/guardians would allow investigators to talk to them about the study. Parents/guardians who were interested in the study would then be referred on to investigators. An explanation of the study, along with an information letter and consent form (Appendix G, H) and a research media records release form (Appendix I), was offered by investigators. Investigators conducted the informed consent discussion and checked whether the parent/guardian understood the information provided. Consent was voluntary and free from coercion. Once consent was obtained, the data were collected when the participating infants had painful and non-painful procedures. If consented infants could not be studied or consent from eligible infants' parents/guardians could not be obtained, organizational reasons (e.g., time constraints) or study reasons (e.g., the inability of parent/guardian to understand English) for nonparticipation were documented in the screening log.

Data collection procedure

After consent was obtained from the parents, the enrolled infant's nurse was informed of the infant's participation in the study. A sign with study name and the investigator's pager number and cell phone number were posted at the bedside of the participating infant. The participating infant was subsequently checked regularly during the potential data collection period to ensure that data collection occurred during one painful and one non-painful procedure.

When a painful or non-painful procedure was scheduled to take place, the enrolled infant's nurse was advised that the infant would be observed during the procedures. Investigators set up the SC device and video camera at least 10 minutes prior to the procedure to ensure the devices were prepared before the data collection. Preliminary data on the SC device and video camera were evaluated to allow calibration or adjustments prior to data collection. The formal data were recorded through the three different phases: before, during and after the procedure, which was defined in the Manuscript Two (Figure 1-5). Participating infants' baseline behavioural state (i.e., active and awake, quiet and awake, active and asleep, quiet and asleep), highest heart rate, lowest oxygen saturation (three indicators of the PIPP-R) were observed 15 seconds prior to formal data collection (i.e., three minutes before a procedure).

Participating infants' demographic and medical information 24 hours prior to observation were collected from infants' health care records by using the data collection form I (Appendix J). The Neonatal Therapeutic Intervention Scoring System (NTISS) was used as a proxy severity of illness score (Appendix K) and recorded in the data collection form I

(Gray, Richardson, McCormick, Workman-Daniels, & Goldmann, 1992; Harrison, 2001; Wu, Lee, Lee, & Chen, 2015). More details about NTISS have been described in Manuscript Two. There was no attempt to standardize painful or non-painful procedures, but details of the procedures and any medication change, patient care or unexpected painful procedures during data collection were recorded by using the data collection form II (Appendix L). After the observation of the painful or non-painful procedure was completed, the highest heart rate and lowest oxygen saturation every 30 seconds before, during and after procedures in the previous time period were extracted from bedside monitoring devices.

Sample size estimation

The sample size was determined to ensure the three primary data analyses had sufficient statistical power. Sample size calculation for the comparison of NWps between painful and non-painful procedures using the Paired t-test was based on one previous study reporting NWps for measuring pain in mechanically ventilated infants: mean NWps: 0.35 (standard deviation=0.26) during heel lance and 0.2 (standard deviation=0.21) at rest (Karpe et al., 2013). The pooled standard deviation was 0.24, resulting in a difference of 0.63, which means the effect size is between medium and large based on Cohen's d (Polit, 2010). Fixing the probability of type I error at 5%, 44 infants would provide 80% power to detect a difference between SC values during painful procedures and non-painful procedures (Polit, 2010). Sample size calculation for the comparison of NWps in the different phases of the procedures, using RM-ANOVA could not be based on any previous study. Thus, the effect size is estimated to be medium (eta-squared=0.06) based on Cohen's conventional values

(Polit, 2010). Fixing the probability of type I error at 5%, 50 infants would provide 80% power to detect a different NWps in the different phase of procedures (Polit, 2010). Sample size calculation for the correlation of NWps with the behavioural observational measures, using Pearson's correlation was based on a study of SC for measurement pain in critically ill children: the correlation between NWps and the behavioural score was reported as 0.57 (Solana et al., 2015). This means the effect size is large based on Cohen's conventional values (Polit, 2010). Fixing the probability of type I error at 5%, 29 infants would provide 80% power to detect a relationship between NWps and the referent pain measures (i.e., PIPP-R and the four-item NFCS) (Polit, 2010). The largest sample size, 50 infants, was used in this study. The sample size was increased to 55 infants to allow for a 10% loss of data due to technical errors in recording or other attrition reasons.

Withdrawal of participants

Infants would be withdrawn from the study if they experienced an adverse event or the HCPs thought it was not appropriate to study the infant anymore. Parents/guardians were also free to withdraw their infant from the study at any time upon their request. When an infant was withdrawn from the study, parents/guardians could choose to allow the research team to have their infant's data already collected in the study kept for analysis or have the investigators destroy all the data. Reasons for withdrawal were recorded in the screening log and master list.

Data Management

The screening information was documented in a screening log. Patient demographic characteristics and medical information were recorded on the paper-based data collection form I (Appendix J) and subsequently entered into an Excel database (Office 365) for Microsoft Windows 10. Other information (e.g., timing of the painful procedure, physiological responses, unexpected events) was recorded on the paper-based data collection form II (Appendix L) and subsequently entered into the database. Facial expression indicators as recorded by video-recording were coded using the PIPP-R (Appendix M) and the four-item NFCS (Appendix N) subset once all the data were collected, and the coding was then entered into the database. SC data were stored using a portable computer, and SC values were calculated once all the data were collected by means of the software analysis package. SC values were entered into the database. All the data in the database were double-checked by a research assistant for accuracy.

Confidentiality of all participating infants and their parents was maintained. Following data collection, infants were identified by a unique Subject Identification Number (SID). All paper-based data collection forms or electronic databases were identified by the SID only. Video recordings were only labeled by SID. No identifying information were presented or published. Variables that can be identifying of the person either alone or in combination were not linked to SIDs. An electronic master list contained the SIDs, date of study, and medical record number, which was password protected and stored on the password protected CHEO disk drive and was only accessed by the investigators involved in this study.

All the data storage and retention were in accordance with CHEO Research Ethics

Board Guidelines. The database and master list were password protected and stored on the password protected CHEO disk drive and could only be accessed by the investigators involved in this study. The screening log was stored on the CHEO disk drive and could also only be accessed by the investigators involved in this study. Hard copies of the completed data collection forms and study data were kept in a locked filing cabinet in the investigator's office in accordance with CHEO policies. Only investigators could have access to the locked filing cabinet. A digital camera was used to record infants during painful or non-painful procedures. At the end of each day, the video files were transferred to a password protected central CHEO drive and erased from the digital video camera. All video files were encrypted and can only be accessed by the investigators involved in this study.

Upon completion of the study (i.e. study closure when all analyses and publications are completed), electronic data will be removed from the password protected computers and stored on an electronic password protected storage device. Paper-based documents and the electronic storage device will be stored in a secured and locked cabinet at the investigator's office. All data will be kept for seven years after the completion of the study as per CHEO REB guidelines. At the end of the data retention period, printed documents will be securely shredded, and electronic data stored on an electronic storage device will be securely reformatted and pulverized.

Benefits and risks to participants

As a cross-sectional observational study, there was no immediate benefit to the participating infants of this study. However, the findings of this study will contribute to the

knowledge of pain assessment and provide a potential accurate method of pain measurement in mechanically ventilated infants, with a potential to positively impact pain management in this vulnerable population.

This was a low-risk study which did not increase risks to the participating infants. Adverse events associated with SC monitoring in infants are very rare and do not differ to that of standard bedside monitoring (Med-Storm Innovation AS, 2012). It was therefore highly unlikely that there would be any adverse events related to SC monitoring in this study population. No interventions were implemented for the purpose of the study, and no attempt to change standards of care was made. Thus, there was no change in treatment or numbers of painful procedures as a result of the study, and the use of the SC device and the camera was not invasive.

Any untoward medical occurrence in an infant enrolled into the study, during the study period (from setting up the SC monitor to completion of data collection) regardless of its causal relationship to SC monitoring, was considered as an adverse event and recorded in the study Adverse Event Form (Appendix O) (Canadian Association of Research Ethics Boards, 2010).

Outline of dissertation

In this chapter, the background, the statement of problem, the study objectives and research design of this dissertation were introduced. The following Chapters 2-3 contain the two manuscripts that present the research findings of this dissertation. The Chapter 4 of this thesis contains: 1) a summary of the findings from the two studies, 2) a discussion of the

findings, 3) the contribution of the findings to the broader literature, 4) the implications of the findings for clinical practice and research, 5) study limitations, 6) a description of knowledge dissemination activities at the end of the project, and 7) the conclusion. The final chapter specifies the primary researcher and each collaborator's distinct contribution to this doctoral dissertation and published papers and/or manuscripts included in the dissertation.

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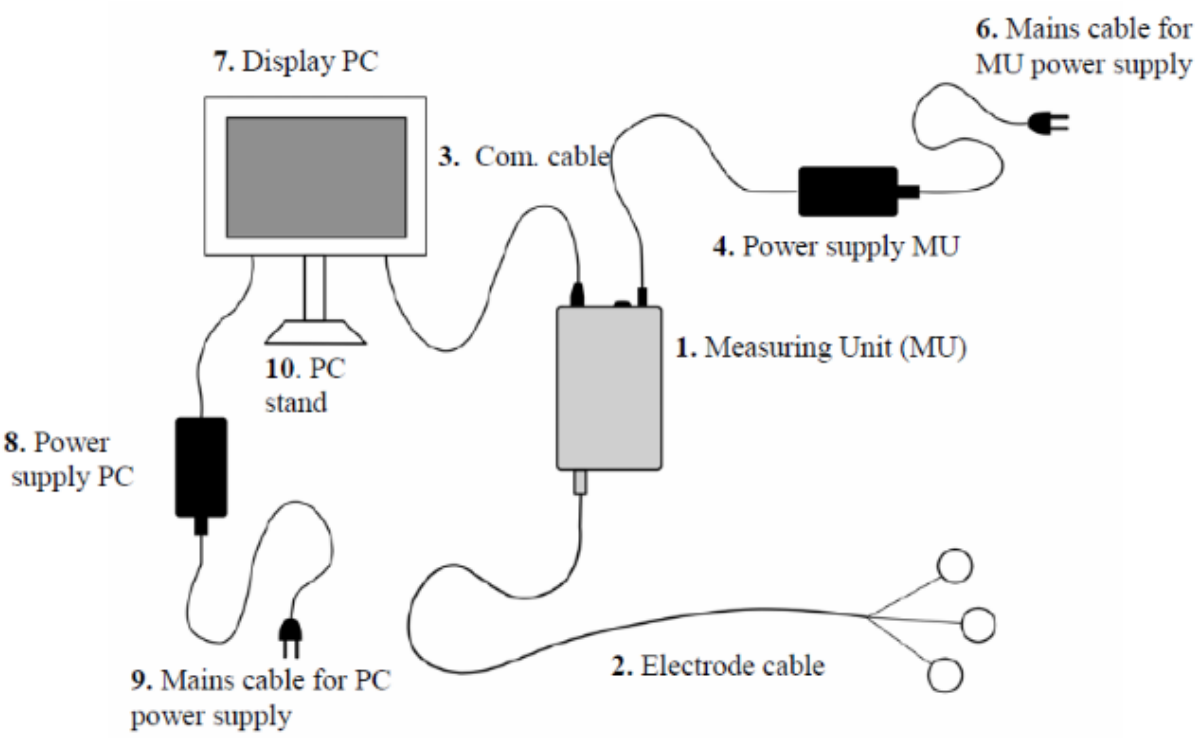

Figure 1- 1. Med-Storm skin conductance monitor

Note:
Med-Storm Innovation AS. (2012). Med-Storm Pain Monitor User Manual. Retrieved November 11th, 2016, from http://www.med-storm.com/pdf/UserManualEnglsihMA00127_20130424.pdf

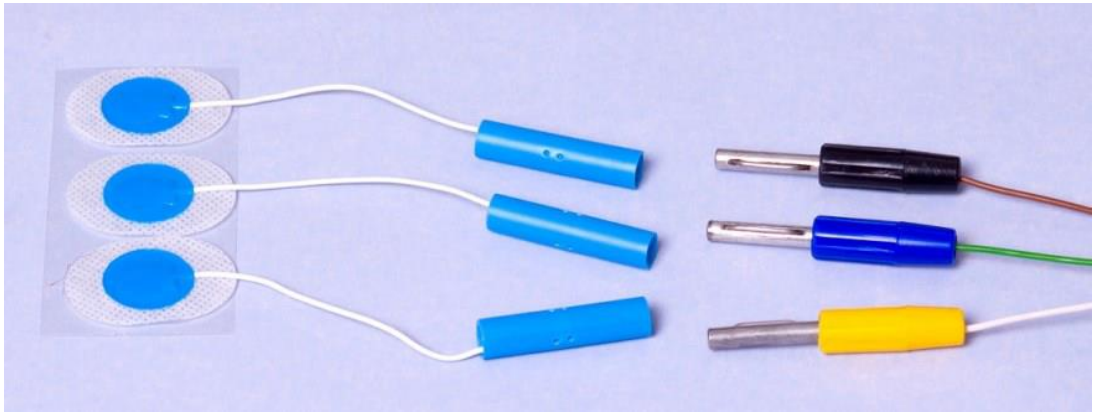

Figure 1- 2. Skin conductance electrodes

Note:
Med-Storm Innovation AS. (2012). Med-Storm Pain Monitor User Manual. Retrieved November 11th, 2016, from http://www.med-storm.com/pdf/UserManualEnglsihMA00127_20130424.pdf

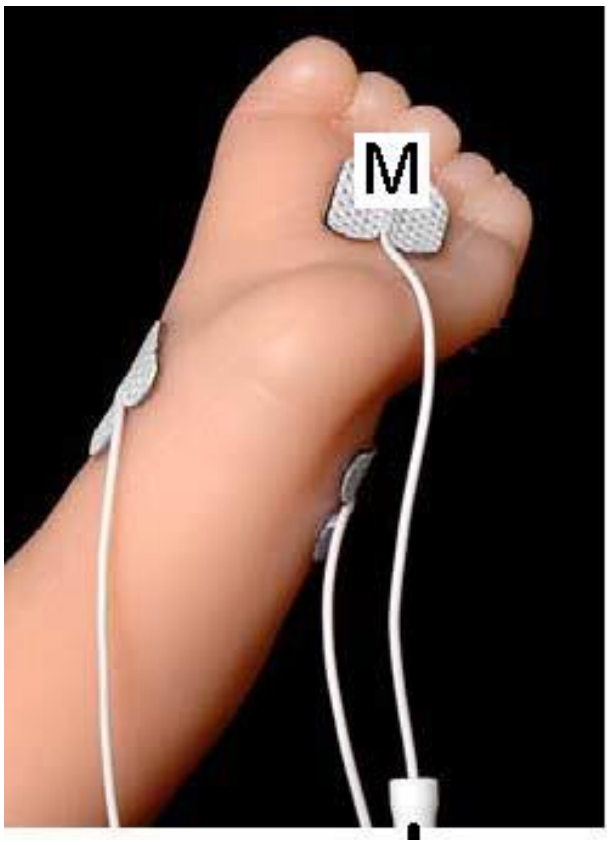

Figure 1- 3. Skin conductance electrodes placement

Note:
Med-Storm Innovation AS. (2012). Med-Storm Pain Monitor User Manual. Retrieved November 11th, 2016, from http://www.med-storm.com/pdf/UserManualEnglsihMA00127_20130424.pdf

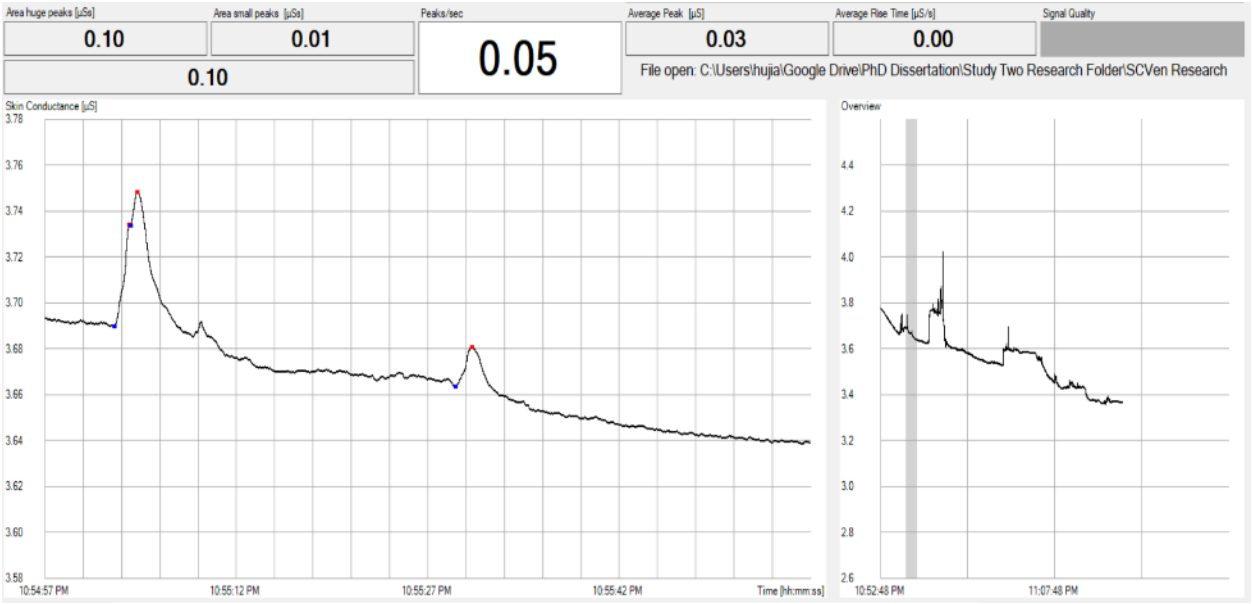

Figure 1- 4. Skin conductance activity and parameters

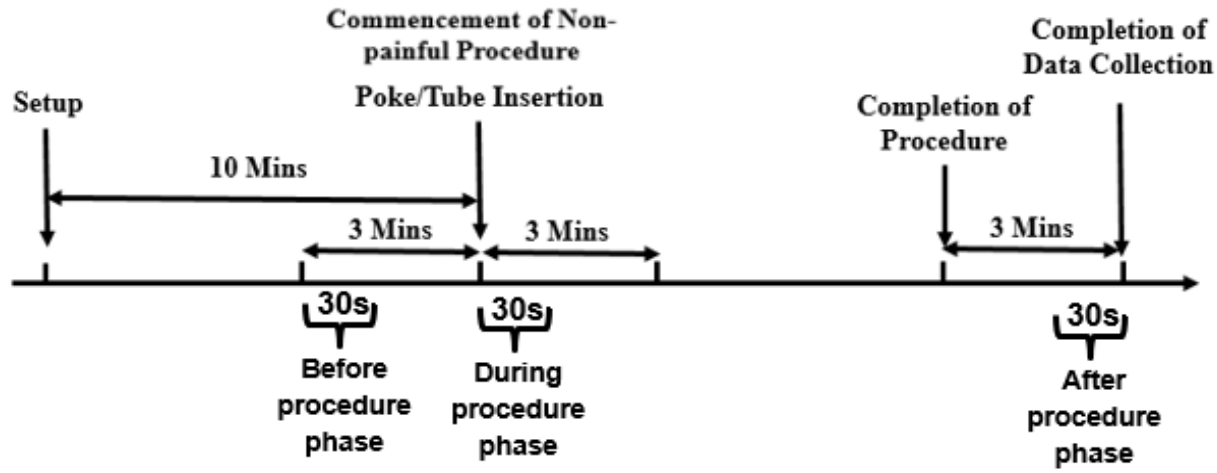

Figure 1- 5. Phases of painful and non-painful procedures

Chapter 2: Manuscript One. The Validity of Skin Conductance for Assessing Acute Pain in Infants: A Scoping Review

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REVIEW ARTICLE

The Validity of Skin Conductance For Assessing Acute Pain in Infants

A Scoping Review

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Objectives: Measuring pain in infants is important but challenging, as there is no "gold standard." The measurement of skin conductance (SC) is considered to be a measure of stress and as a surrogate indicator of pain. The objectives of this study were to identify the extent of research conducted and to synthesize the validity evidence of SC for assessing acute pain in infants.

Methods: The Arksey and O'Malley framework for scoping reviews was followed, and 9 electronic databases were searched. Data were analyzed thematically and presented descriptively including the following main categories: study information/details, sampling information, characteristics of participants and settings, SC outcome measures, and validity evidence.

Results: Twenty-eight studies with 1061 infants were included, including 23 cross-sectional observation studies and 5 interventional studies. The most studied infants were those with mild severity of illness (n = 13) or healthy infants (n = 12). The validity evidence of SC was tested in relation to referent pain measures (13 variables), stimuli (13 variables), age (2 variables), and other contextual variables (11 variables). SC was not significantly correlated with vital signs, except for heart rate in 2 of the 8 studies. SC was significantly correlated with the unidimensional behavioral pain assessment scales and crying time rather than with multidimensional measurements. Fourteen of 15 studies (93.3%) showed that SC increased significantly during painful procedures.

Conclusions: Inconsistent findings on validity of SC exist. Future research should aim to identify the diagnostic test accuracy of SC compared with well-accepted referent pain measures in infants, study the validity evidence of SC in critically ill infants, and utilize rigorous research design and transparent reporting.

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Key Words: infant, newborn, pain measurement, acute pain, galvanic skin response

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The effective management of pain in infants, and determining appropriate analgesia dosing, depend on measuring pain in a valid and reliable manner.[1,2] Pain measurement refers to the assignment of a numerical value to quantify the intensity of pain, which is one of the important tasks in pain assessment.[1] Although tremendous advances have been made in understanding pain experience and > 4 dozen pain measurement tools have been established for infants, measuring pain in infants remains complex and challenging for researchers and clinicians.[3–5] One of the key challenges in infant pain measurement is the lack of a "gold standard" for measuring pain, as infants are unable to give a self-report.[6,7] Behavioral, physiological, and multidimensional pain measurement methods are, therefore, considered as surrogate approaches for self-report, for example, Neonatal Facial Coding System, heart rate (HR), and Premature Infant Pain Profile.[4,8,9]

Although behavioral indicators of pain are widely used as part of most pain assessment scales to assess pain in hospitalized infants, there are significant limitations when using these indicators in infants who are critically ill, especially in those infants requiring respiratory support in intensive care units. The airway tube, tube holder, and tape over the infants' faces may limit the clinicians' view and accurate assessment of the infants' facial expressions.[10] It is difficult to assess body movements, as critically ill infants, especially neonates, may be restrained to avoid accidental removal of medical devices, swaddled, or they may lack sufficient energy to demonstrate body movements.[11] Neuromuscular blockers or deep sedation may also be used in clinical settings to reduce critically ill infants' resistance to ventilation or other treatments, if needed. These medications could preclude facial expressions and body movements.[12]

There is growing interest in the role of the cerebral cortex in pain neurophysiology and transmission of noxious stimuli from the nociceptors to the central nervous system.[13] The majority of studies have been conducted in animals;[14] however, a recent systematic review synthesized the evidence of neurophysiological methods used in infant acute pain assessment.[15] In this review, 9 studies were identified using near-infrared spectroscopy, 8 studies using electroencephalography, and 2 studies using functional magnetic resonance imaging.[15] The findings showed great variability

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of methodologies used in the studies and found that there was no definitive conclusion in the usefulness of these novel noninvasive cortical indicators for pain assessment.[15] Thus, pain measurement using cortical indicators is an emerging area of research but is far from being applicable in clinical settings.[14]

Changes in vital signs such as HR, blood pressure, respiratory rate, and oxygen saturation are used as single indicators of pain or in combination with facial expressions, body movements, and/or contextual indicators of pain as multidimensional pain measurement.[16] However, these vital signs are affected by many factors other than pain, such as pulmonary and cardiovascular diseases, mechanical ventilation, cardioactive and vasoactive drugs, and circulatory changes.[1,12,17] Many clinical practice guidelines recommended that clinicians should minimize emphasis on vital signs, as studies using vital signs to indicate the presence of pain in neonates, infants, children, adolescents, and adults all have inconsistent findings.[1,12,17] In addition, a recent systematic review demonstrated that evidence using cardiovascular indices of response (ie, mean HR, HR change, or HR variability) to acute pain in infants is still limited.[18]

The measurement of skin conductance (SC) is a physiological approach to measuring pain, which is based on the sympathetic nervous system's response to stress.[19] When pain occurs, its associated stress induces sympathetic excitation and emotional sweating at an infant's palmar (hand) or plantar (foot) regions.[20] With filling and absorption of sweat in the sweat glands, the SC measurement device monitors the increasing and decreasing electrodermal activity.[21] In general, the SC parameters include mean skin conductance level (SCL), number of waves per second (NWps), area under the curve, area huge peaks, area small peaks, average rise time, and average peak. These parameters are defined in Appendix A (Supplemental Digital Content 1, http://links.lww.com/CJP/A568). Higher values in any of the above SC parameters are indicative of higher stress.[21] Utilizing SC to measure pain in infants is more objective than using facial expressions or body movements, especially in critically ill infants. The SC measurement device is quick and straightforward to use, requires a short training time, and the scores of SC can be easily and quickly understood by clinicians and researchers.

The first study using SC for assessing pain in the clinical setting was published in 1982, wherein SC was used in adults undergoing general anesthesia.[22] Since this first study, many papers have been published using SC for assessing pain, including 2 published reviews. The first review discussed the benefits and challenges of using the SC measurement device from Med-Storm Innovations,[23] and the second review narratively summarized the capability of SC for assessing pain compared with other physiological pain assessment methods in children.[24] However, research on the use of SC for assessing acute pain in infants has not been systematically identified and synthesized. Thus, in this study we conducted a scoping review to identify the extent of research conducted and to synthesize the validity evidence of SC for assessing acute pain in infants.

METHODS

Research Design

This scoping review followed Arksey and O'Malley scoping review framework, consisting of the 5 stages outlined below, which is widely used in health care studies.[25–27] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-Scoping Review was used to report this study.[28] The scoping review was registered in PROSPERO (2016: CRD42016036142).

Stage 1: Identifying the Research Question

The research question was "what is the validity evidence of SC for assessing acute pain in infants in the literature and how have the validation studies been done." Studies using SC for assessing acute pain in newborns or infants up to 12 months of age were eligible for inclusion. For studies including both infants and older children, the results of infants were separated from other populations if possible, or the study authors were contacted to request the infant data. If infant data could not be separated, the article was excluded.

The concept of validity was based on the Standards for Educational and Psychological Testing, which are considered best practice in the field of psychometrics.[29,30] In the Standards, construct validity is the central component in validation work and encompasses the sources of evidence germane to the validation of the interpretation and use of the score of an instrument.[29,31] There are 4 sources of construct validity evidence, including content, response processes, internal structure, and relations to other variables.[27] Content evidence refers to whether the items in a measure cover the content of the construct being measured.[27] Response processes evidence refers to how respondents interpret, process, and answer the items.[27] Internal structure evidence refers to how the items relate to one another. Relational evidence refers to what the relationship is between scores obtained with a measure and other variables, which the score is (or is not) expected to relate.[27] As SC is an objective physiological indicator, validity in content, response process, and internal structure are not applicable. In this scoping review, studies validating SC for pain assessment or using SC as a measurement during observation or interventions were included and analyzed in this review to generate the validity evidence of SC in relation to referent pain measures, stimuli, age, and other contextual variables.

Stage 2: Identifying Relevant Studies

The research question and purpose guided the search strategy in this review (Appendix B, Supplemental Digital Content 2, http://links.lww.com/CJP/A569). The search strategy was developed by the research team and a librarian experienced in systematic review searching, and it was peer reviewed by a second librarian using the Peer Review of Electronic Search Strategies.[32] In addition, reference lists of all identified articles were screened and reviewed for eligibility.

Searches of the following databases were used to identify relevant literature: MEDLINE (OVID), EMBASE (OVID), PsycINFO (OVID), and CINAHL (EBSCO). Other literature resources were also searched, including ProQuest Dissertations and Theses Global, ClinicalTrials.gov (www.clinicaltrials.gov), metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), Google, and Google Scholar (the first 10 pages of each). All these databases were searched up to August 11, 2018. Search terms included "Pain*," "Nocicept*," "Stress*," "Cutaneous (conduct* or response* or resistan*)," "Skin (conduct* or response* or resistan*)," "Electrodermal

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(conduct* or response* or resistan*)," "Galvanic (conduct* or response* or resistan*)."

Stage 3: Study Selection

After duplicates were removed, a 2-step screening was conducted by 2 reviewers. In the first step, the 2 reviewers (J.Hu, S.M.) independently screened the titles and abstracts of all studies to determine their potential eligibility for the review using the online software Covidence.[33] All potentially relevant records and those records that did not contain enough information to determine eligibility (eg, no available abstract) were retained. In the second step, the same 2 reviewers independently read the full text of all potentially relevant articles to determine eligibility for inclusion in the review. The reviewers met at the beginning, midpoint, and final stages of each step to discuss challenges and uncertainties related to study selection. As determined a priori, any conflicts in the identification of relevant studies during either the first or second step were resolved through a consensus process or by consulting a third senior reviewer (D.H.), as required. Reasons for exclusion were documented for all papers excluded from the review at this second step.

Stage 4: Data Extraction

This stage consisted of collecting data according to key issues and themes covered by the research question and purpose.[25] Using data extraction forms developed by the research team, data were extracted on author, year of publication, journal, aims of the study, country of origin, study design, sample size, setting, data collection methods, outcome measures, and validity evidence (Table 1). Data from included studies were extracted by 1 reviewer (J.Hu) and double-checked by a second reviewer (S.M.) for accuracy.[61] Discrepancies in data extraction were resolved through consensus.

A formal assessment of methodological quality of the included studies was not performed in this study. The tools or standards developed to evaluate the quality of observational or interventional studies include items with regard to the validity of the measurement, which was the objective of this scoping review.[62] Moreover, scoping reviews aim to determine the extent of the research available with regard to a topic and the way the research has been conducted, as opposed to conducting quality appraisals to identify studies at the least risk of bias or the high-quality evidence to answer a particular question.[25,63,64] Hence, the included studies were not evaluated for methodological quality. Instead, we focused on performing a comprehensive assessment of the validity evidence of SC for assessing infant pain in each study.

Stage 5: Collating, Summarizing, and Reporting the Results

Data were analyzed thematically and presented under the following main categories: general information of publication (author, year of publication, and journal), sampling information (sampling methods, sample size calculation, actual sample size, and reasons for missing data), characteristics of participants and settings (country of origin, clinical setting, health status, gestational age, postnatal age, sex, birth weight, medication, stressful stimuli, and other information), SC outcome measures (apparatus, parameters, and data collection and analysis methods), and validity evidence (eg, relationships to referent pain measures).

RESULTS

A total of 6409 titles and abstracts were screened, 194 full-text papers were reviewed, and then 166 were excluded. As shown in Appendix C (Supplemental Digital Content, http://links.lww.com/CJP/A570) the majority were excluded at full text because of any of the following reasons: (1) SC was not used (n of studies = 69), (2) SC was not used for assessing pain (n = 47), or (3) SC was used for pain assessment in adults (n = 29). The final sample comprised 28 studies with 1061 infants (Fig. 1). The majority of included studies (n = 23[19,34–37,39–51,55,56,58–60]) used a cross-sectional observation design to validate SC for pain assessment, and the other 5 were interventional studies, of which SC was an outcome measure.[38,52–54,57] Studies were conducted in 14 countries, with most conducted in Norway (n = 7[34–38,54,60]), followed by Brazil (n = 3[42,51,56]), and 2 studies from each of the following countries: United States,[41,45] the Netherlands,[47,57] Australia,[39,43] Italy,[44,50] Sweden,[40,48] and Turkey.[53,58] The earliest study was published in 1990,[19] and the remaining studies were published between 2000 and 2016. The majority of studies were published after 2010 (n = 20[41–60]). Details on characteristics of included studies are given in Table 1.

Participants and Settings

Studies were conducted in special care nurseries (n = 10[19,34,35,38,44,45,55,56,58,59]), neonatal intensive care units (n = 10[39,41,43,46,47,49,53–55,60]), mother–baby units (n = 6[36,37,40,42,50,51]), immunization clinics (n = 2[36,37]), the operating room (n = 1[57]), the delivery room (n = 1[52]), and the postanesthesia care unit (PACU) (n = 1[48]). Three studies included 2 settings, mother–baby units and immunization clinics (n = 2[36,37]), and special care nurseries and neonatal intensive care units (n = 1[55]).

Eleven studies focused on a population of term infants,[37,40,42,43,50,51,53,56,58,59] 10 studies included preterm infants (22 to 36 wk gestation),[34–36,38,41,45,52,54,57,60] and 7 studies included both term and preterm infants.[19,39,44,46,47,49,55] Most studies were conducted with healthy infants (n = 12[19,34–38,40,42,50,51,56,59]) and infants with mild severity of illness who were breathing spontaneously with no analgesics, sedation, or neuromuscular blockers (n = 13[39,41,43–48,53–55,58,60]). Only 3 studies included infants receiving analgesics, sedatives, or neuromuscular blockers.[49,52,57] In Karpe et al's[49] study, 32 mechanically ventilated infants were receiving continuous intravenous infusions of midazolam (0.2 mg/kg/h) and/or fentanyl (2 to 3 μg/kg/h). Baleine et al's[52] study included 27 newborn infants receiving nasal midazolam before intubation. van der Lee et al[57] studied 22 infants receiving propofol (2 mg/kg) or morphine (0.1 mg/kg) with vecuronium (0.1 mg/kg) before intubation. Two studies used validated tools to measure severity of illness, including Neonatal Therapeutic Intervention Scoring System (NTISS, n = 1[43]) and Neonatal Acute Physiology Scores (NAPS, n = 1[60]).

Most studies did not report sampling methods, and convenience sampling was reported in 4 cross-sectional studies[42,46,50,56] and 4 randomized controlled trials.[38,53,54,57] Only 1 study reported the method of determining sample size.[51] Twelve studies with 293 infants reported the reasons for missing data,[37,39,40,42–44,48,52,54,56,57,59] all of which were due to technical issues of the SC measurement device or electrodes (n of infants = 27, 9.2%), leading to recording loss (n = 7), low quality of measured SC (n = 9), collection failure (n = 10), and electrodes not secured to the skin (n = 1).

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TABLE 1. Characteristics of Included Studies and Participants

	References	Country	Setting	Procedure Studied	Infant Age	Health Condition	Sample N	Missing Data in Analysis
1	Gladman, 1990[19]	Britain	SCN	Heel lance	GA: 25-42 wk PNA: 1-73 d	Healthy	82	NR
2	Storm, 2000[34]	Norway	SCN	Heel lance	GA: 29-35 w PNA: 1-25 d	Healthy	20	NR
3	Storm, 2001[35]	Norway	SCN	Heel lance	GA: 29-34 wk PNA: 2-29 d	Healthy	50	NR
4	Hellerud, 2002[36]	Norway	MU; IC	Heel lance; nursery handling	GA: 29-42 wk PNA: 1-3 mo	Healthy	71	NR
5	Hernes, 2002[37]	Norway	MU; IC	Auditory stimuli	GA: > 37 wk PNA: 1 d-12 mo	Healthy	42	3 recording losses
6	Storm, 2002[38]	Norway	SCN	Heel lance	GA: 27-35 wk PNA: 2-29 d	Healthy	48	NR
7	Harrison, 2006[39]	Australia	NICU	Heel lance; diaper change	GA: 25-42 wk PNA: 1-123 d	Complex medical, surgical, genetic, and metabolic	22	1 electrode not secured to skin
8	Eriksson, 2008[40]	Sweden	MU	Heel lance; nursery handling	GA: 38-42 wk PNA: 3-5 d	Healthy	27	2 low quality of SC assessments 3 collection failures
9	Salavitabar, 2010[41]	United States	NICU	Auditory stimuli	GA: 29-33 wk PNA: <6 h	Respiratory and circulatory stable	11	NR
10	de Jesus, 2011[42]	Brazil	MU	Heel lance	GA: 37-41 wk PNA: <48 h	Healthy	41	2 low quality of SC assessments
11	Roeggen, 2011[43]	Australia	NICU	/	GA: 37-40 wk PNA: 12-40 d	NTISS 6-13; not having cardiorespiratory support, mechanical ventilation, inotropic support, surgery	15	2 collection failures
12	Cresi, 2012[44]	Italy	SCN	/	GA: 33-41 wk PNA: 17-46 d	Symptoms of GERD	12	3 low quality assessments of SC
13	Munsters, 2012[45]	Sweden	SCN	Heel lance; Tactile stimuli, (feeding +stethoscope)	GA: 22-34 w PNA: 1-47 d	Respiratory and circulatory stable	10	NR
14	Pereira-da-Silva, 2012[46]	Portugal	NICU	Heel lance	GA: 24-41 wk PNA: 1-96 d	Postsurgery; not having mechanical ventilation	16	NR
15	Valkenburg, 2012[47]	The Netherlands	NICU	/	GA: 29-38 wk PNA: 13-76 d	Postsurgery; not having mechanical ventilation	11	NR
16	Dalal, 2013[48]	United States	PACU	/	GA: full-term PNA: 6–12 mo	Postoperative recovery; not having mechanical ventilation	31	NR
17	Karpe, 2013[49]	Poland	NICU	Arterial blood sampling; airway suctioning	GA: 34-39 wk PNA: NR	Mechanical ventilation	32	NR
18	Scaramuzzo, 2013[50]	Italy	MU	/	GA: full-term PNA: <48 h	Healthy	158	NR
19	Tristao, 2013[51]	Brazil	MU	Heel lance	GA: 37-41 wk PNA: <48 h	Healthy	36	NR
20	Baleine, 2014[52]	France	DR	Intubation	GA: 27-33 wk PNA: 1 d	Requiring semi-elective intubation	27	NR
21	Beken, 2014[53]	Turkey	NICU	Venipuncture	GA: 37-41 wk PNA: > 14 d	Neonatal jaundice; respiratory and circulatory stable	25	NR
22	Lyngstad, 2014[54]	Norway	NICU	Diaper change	GA: 28-34 wk PNA: 24-33 d	Respiratory and circulatory stable	17	2 collection failures
23	Macko, 2014[55]	Czech Republic	NICU; SCN	/	GA: 25-41 wk PNA: NR	Respiratory and circulatory stable	57	NR
24	de Jesus, 2015[56]	Brazil	SCN	Heel lance	GA: 37-41 wk PNA: <48 h	Healthy	41	2 low quality assessments of SC
25	van der Lee, 2015[57]	The Netherlands	OR	Intubation	GA: 26-34 wk PNA: 0-3 d	Requiring semi-elective intubation	22	3 recording losses
26	Gokulu, 2016[58]	Turkey	SCN	Painful stimuli (heel lance, venous blood sampling, intramuscular injections)	GA: 37-41 wk PNA: 24-30 h	Two groups: receiving at least 6 painful procedures and receiving 1 painful procedure	60	NR

(*Continued*)

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TABLE 1. (*continued*)

References	Country	Setting	Procedure Studied	Infant Age	Health Condition	Sample N	Missing Data in Analysis
27 Schubach, 2016[59]	Germany	SCN	Heel lance	GA: 37-40 wk PNA: 1-11 d	Two groups: NAS and non-NAS	24	NR
28 Zeiner, 2016[60]	Norway	NICU	Morning nursing care (axillary temperature, assessment, diaper change)	GA: 28-35 wk PNA: 4-5 d	NAPS: mild severity of illness	30	NR

/ indicates no procedures studied; DR, delivery room; GA, gestational age; GERD, gastroesophageal reflux disease; IC, immunization clinics; MU, maternity unit; NAPS, Neonatal Acute Physiology Scores; NAS, neonatal abstinence syndrome; NICU, neonatal intensive care unit; NR, not reported; NTISS, Neonatal Therapeutic Intervention Scoring System; OR, operating room; PACU, postanesthesia care unit; PNA, postnatal age; SC, skin conductance; SCN, special care nurseries.

Details on characteristics of the infants included in the studies are given in Table 1.

SC Measures

The SC measurement device from Med-Storm Innovations was the most commonly used device (n = 26[34–58,60]), and Dr Storm was the first author or coauthor of 15 of these studies.[34–44,46,54,56,60] Various SC parameters were used; however, the NWps was consistently used in all studies, except the first study in 1990.[19] Sixteen studies reported preparation time to set up the SC measurement device and stabilize the SC values, ranging from 60 seconds to 30 minutes.[19,34,38–41,43,45,47,49,51,54,56,58–60] Time windows of calculating SC values were reported in 10 studies,[42,44,45,47,48,50,52,54,56,57] and 15 seconds were most frequently used (n = 6[42,50,52,54,56,57]). Most studies reported time

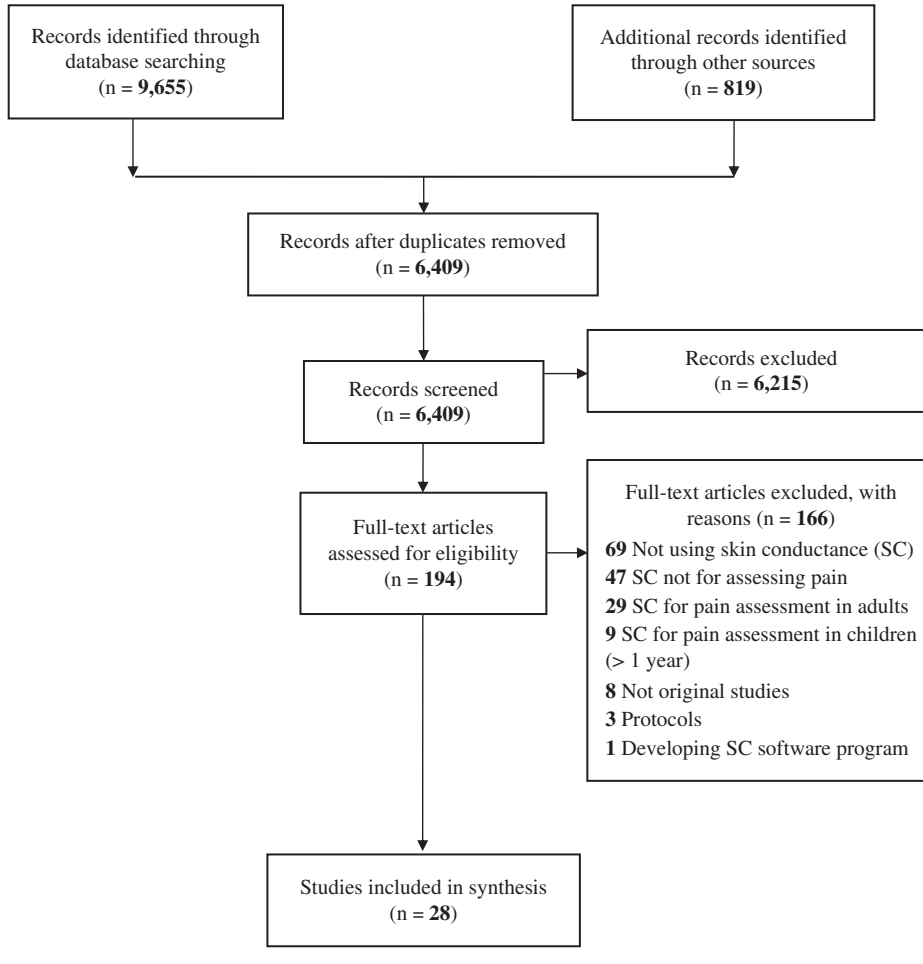

FIGURE 1. PRISMA flow diagram.

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windows of collecting SC data (n = 23[19,34–41,43,45,46,48,51–60]), but these varied from 20 minutes before procedures to 60 minutes following arrival to the PACU. Only 1 study reported the sampling method used to obtain SC values to represent pain intensity in a specific period of time[54]; Lyngstad et al's[54] study reported using the maximum SC value 5 minutes before, during, and 5 minutes after diaper change. Details on the SC measures reported in the included studies are given in Table 2.

Validity Evidence of SC for Pain Assessment

In the included studies, validity of SC for pain assessment was assessed in relation to 39 variables, which are categorized into 4 domains: referent pain measures (13 variables), stimuli (13 variables), age (2 variables), and other contextual variables (11 variables). Statistical significance of results is presented in Table 3, and details of the statistical tests are presented in Appendix D (Supplemental Digital Content 4, http://links.lww.com/CJP/A571).

Relationships to Referent Pain Measures

Twenty studies tested validity evidence of SC in relation to referent pain measures.[19,34,35,37,38,40–43,45,48,50,51,53–56,58–60] The referent pain measures included 3 vital signs (HR,[38,41–43,54,55,58,60] respiratory rate,[41,60] and oxygen saturation[41–43,54,55,58]); crying time[38]; 2 scales for state of arousal and general movements (Prechtl Scale[19,34,35,37,38,42,55,59] and Newborn Individualized Developmental Care and Assessment Program [NIDCAP][41,60]); 3 unidimensional measures (Neonatal Facial Coding System (NFCS),[48,56] COMFORT Behavior Scale (COMFORT-b),[51,56] and ABC Pain Scale[50]); and 5 multidimensional measures (Neonatal Pain Agitation and Sedation Scale [N-PASS],[45] Neonatal Infant Pain Scale [NIPS],[53,56,58] Premature Infant Pain Profile [PIPP][40], and Bernese Pain Scale for Neonates [BPSN][59]).

HR (n = 8[38,41–43,54,55,58,60]) and Prechtl Scale (n = 8[19,34,35,37,38,42,55,59]) were the 2 most commonly used surrogate pain measures. Five of the 8 studies that included Prechtl Scale showed a statistically significant positive relationship between SC and Prechtl Scale,[19,35,37,38,59] but only 2 of the 8 studies that included HR showed significant positive associations of SC with HR.[38,41] The associations of SC with NFCS[48,56] and COMFORT-b[51,56] were tested in 2 studies, respectively; however, only 1 study of each reported statistically significant positive associations.[48,51] A statistically significant positive relationship was reported between SC and the ABC Pain Scale[50] and crying time.[38] No studies reported that changes of SC were significantly associated with oxygen saturation,[41–43,54,55,58] respiratory rate,[41,60] NIDCAP,[41,60] NIPS,[53,56,58] PIPP,[40] N-PASS,[45] and BPSN.[59]

Only 1 study analyzed diagnostic test accuracy (cutoff point to detect pain, sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) of the SC measures compared with the NFCS.[48] This single study showed that NWps (cutoff point, 0.571), average peak (0.042), and SCL (16.8) had a sensitivity of 54.5%, 90.9%, and 63.6%, respectively, and a specificity of 79.4%, 51.4%, and 63.5%, respectively, to detect moderate or severe pain (NFCS > 4) in infants in the PACU.[48] This performance resulted in PPVs of 21.4% (NWps), 16.1% (average peak), and 15.2% (SCL) and NPVs of 94.4% (NWps), 98.2% (average peak), and 94.4% (SCL).[48]

Relationships to Stimuli

Twenty studies[34,36–42,45,46,49,51–54,56–60] tested validity evidence of SC in relation to stimuli, including painful (n = 16[34,36,38–40,42,45,46,49,51–53,56–59]) and nonpainful procedures (n = 8[36,37,39–41,45,54,60]). There were 2 types of painful procedures: skin-breaking procedures (n = 14), including heel lance (n = 12[34,36,38–40,42,45,46,51,56,58,59]), venipuncture (n = 1[53]), venous (n = 1[58]) or arterial blood sampling (n = 1[49]), and intramuscular injection (n = 1[58]), and traumatic procedures (n = 3), including intubation (n = 2[52,57]), and airway suctioning (n = 1[49]). Most studies identified the type of painful procedure; however, Gokulu et al[58] included 3 different skin-breaking procedures but did not differentiate the specific type of skin-breaking procedures. Nonpainful procedures included diaper change (n = 2[39,54]), morning care (n = 1[60]), including axillary temperature, assessment and diaper change, nursery handling (n = 2[36,40]), feeding plus stethoscope auscultation (n = 1[45]), and auditory stimuli (n = 2[37,41]).

Most studies reported that painful (14/15, 93.3% [34,36,38,39,42,45,46,49,51–53,56,58]) or nonpainful procedures (5/7, 71.4%[36,37,41,54,60]) led to a significant SC increase. Two studies compared SC during different types of procedures (painful vs. nonpainful) and both found infants had significantly higher SC during painful procedures than nonpainful procedures.[36,40] The impact of different purposes of heel lance (blood being drawn for blood gas analysis compared with glycemic testing, requiring a smaller volume of blood) on SC was tested in 1 study and was found to be not significant in terms of NWps but significant in terms of area small peaks and average rise time.[46]

Relationships to Age

The associations between SC and both gestational age (n = 10[34,36,42,43,45,46,51,55,56]) and postnatal age (n = 9[36,37,41,42,45–47,51,53]) were tested using correlation or regression statistical methods; however, only 1 study found significant relationships between postnatal age and SC (NWps and area under curve) in 20 premature infants, who were born between 29 and 35 weeks' gestational age and at the time of the study were between 1 and 25 days postnatal age.[34] Three other studies categorized age into different groups.[19,36,45] Gladman and Chiswick[19] found full-term newborns had higher SCL than preterm newborns. Munsters et al[45] did not demonstrate a difference of SC in different gestational age and postnatal age groups based on a cutoff of 28 weeks' gestational age and 28 days' postnatal age. Hellerud and Storm[36] compared 4 different groups of infants: preterm and full-term newborn infants in the first week of life, and preterm and full-term infants in the postneonatal period (defined in the study as more than 1 week old). After multiple comparisons, statistically significant differences were found between the following 2 groups: preterm infants had higher SCL, but lower NWps and area under curve values than full-term infants in the postneonatal period; full-term newborn infants (defined in the study as less than 1 week old) had higher area under curve values than full-term infants in the postneonatal period (defined in the study as more than 1 week old).[36]

Relationships to Other Contextual Variables

Eleven demographic or medical variables were used in the studies to test the relationship between SC and other variables. Seven studies examined the association between sex and SC,[37,40–42,46,56,59] of which only 2 studies[41,46] found

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TABLE 2. SC Measures

	References	Apparatus	Preparation Time	SC Parameters	SC Calculation Time Window	SC Collection Time Window
1	Gladman, 1990[19]	SC meter	15 min	SCL	NR	Before, during, and 10 min after the heel prick
2	Storm, 2000[34]	Med-Storm Innovations	10 min	SCL, NWps, AUC	NR	3 min before, during, and 3 min after the procedure
3	Storm, 2001[35]	Med-Storm Innovations	NR	SCL, NWps, AUC	NR	2 min before, during, and 2 min after the procedure
4	Hellerud, 2002[36]	Med-Storm Innovations	NR	SCL, NWps, AUC	NR	2-3 min before, during, and 2-3 min after the procedure
5	Hernes, 2002[37]	Med-Storm Innovations	NR	SCL, NWps, AUC	NR	5 s before, and 15 s after the auditory stimuli
6	Storm, 2002[38]	Med-Storm Innovations	10 min	SCL, NWps, AUC	NR	2 min before, during, and 5 min following completion of the procedure
7	Harrison, 2006[39]	Med-Storm Innovations	5 min	SCL, NWps, AUC	NR	5 min before, during, and 5 min following completion of the blood collection
8	Eriksson, 2008[40]	Med-Storm Innovations	60 s (1st); 5 min (2nd)	SCL, NWps, AUC	NR	Before, during, and 3 min after procedure
9	Salavitabar, 2010[41]	Med-Storm Innovations	2 min	NWps	NR	20-30 s before, 20-30 s during, and 20-30 s after sound stimulus
10	de Jesus, 2011[42]	Med-Storm Innovations	NR	NWps, AUC	15 s	NR
11	Roeggen, 2011[43]	Med-Storm Innovations	10 min	NWps	NR	At least 6 periods of monitoring (at least 30 min for each period) in a 48-h period
12	Cresi, 2012[44]	Med-Storm Innovations	NR	NWps, AUC, AHP, ASP	120 s	NR
13	Munsters, 2012[45]	Med-Storm Innovations	5 min	SCL, NWps, AUC	30 s	Heel lance: 1 min before glucose, 2 min after heel lance and squeezing Orogastric tube: a couple of minutes after placement Feeding: at least 3 min after feeding
14	Pereira-da-Silva, 2012[46]	Med-Storm Innovations	NR	NWps, ASP, ART	NR	last 30 s before, 30 s after starting, and last 30 s after the end of blood sampling
15	Valkenburg, 2012[47]	Med-Storm Innovations	5-10 min	NWps	1 h	NR
16	Dalal, 2013[48]	Med-Storm Innovations	NR	SCL, NWps, AP	5 s	15, 30, 45, 60 min following arrival to the PACU
17	Karpe, 2013[49]	Med-Storm Innovations	20 min	NWps	NR	NR
18	Scaramuzzo, 2013[50]	Med-Storm Innovations	NR	NWps	15 s/2 min	NR
19	Tristao, 2013[51]	Med-Storm Innovations	10 min	NWps, AUC	NR	3 min before, during, and 15 s, 30 s, and 180 s after the procedure
20	Baleine, 2014[52]	Med-Storm Innovations	NR	NWps	15 s	2 min before nasal midazolam instillation to 2 min after intubation
21	Beken, 2014[53]	Med-Storm Innovations	NR	NWps	NR	First 30 s during venipuncture and 30 s at the end of venipuncture
22	Lyngstad, 2014[54]	Med-Storm Innovations	15 min	NWps	15 s	5 min before, during, and 5 min after the diaper change
23	Macko, 2014[55]	Med-Storm Innovations	NR	NWps, AUC, AHP, ASP	NR	2 min before, during, and 3-5 min after stimuli
24	de Jesus, 2015[56]	Med-Storm Innovations	10 min	NWps, AUC	15 s	3 min before, 3 min immediately after puncture, 3 min after the end of the procedure
25	van der Lee, 2015[57]	Med-Storm Innovations	NR	NWps	15 s	60 s baseline, 30 mins after completion of the intubation procedure
26	Gokulu,2016[58]	Med-Storm Innovations	5 min	NWps	NR	15 s before and 30 s and 45 s after heel prick
27	Schubach, 2016[59]	Portable Biosignal Recorder Va	30 min	SCL, NWps, AUC	NR	10 min before and 15 s after skin-breaking procedure
28	Zeiner, 2016[60]	Med-Storm Innovations	20 min	NWps	NR	20 min baseline, during nurse handling, and 30 min postinteraction

AHP indicates area huge peaks; AP, average peak; ART, average rise time; ASP, area small peaks; AUC, area under the curve; NR, not reported; NWps, number of waves per second; PACU, postanesthesia care unit; SC, skin conductance; SCL, mean skin conductance level.

differences in SC between male and female infants. Salavitabar et al[41] showed that female infants had higher NWps than male infants, using the independent sample *t* test, but Pereira-da-Silva et al[46] reported the opposite findings using multivariate logistic regression analysis. No statistically significant relationships were found between SC and variables of delivery

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TABLE 3. Validity Evidence of SC

	N	SCL	NWps	AUC	AHP	ASP	ART	AP
A. Pain measures								
1. Heart rate	8	Sig: 1[38]	Sig: 2[38,41] N-Sig: 6[42,43,54,55,58,60]	Sig: 1[38] N-Sig: 3[42,43,55]	N-Sig: 1[55]	N-Sig: 1[55]	/	/
2. Prechtl Scale	8	Sig: 5[19,35,37,38,59]	Sig: 4[35,37,38,59] N-Sig: 3[34,42,59]	Sig: 4[35,37,38,59] N-Sig: 3[34,42,59]	N-Sig: 1[55]	N-Sig: 1[55]	/	/
3. Oxygen saturation	6	/	N-Sig: 6[41–43,54,55,58]	N-Sig: 3[42,43,55]	N-Sig: 1[55]	N-Sig: 1[55]	/	/
4. NIPS	3	/	N-Sig: 3[53,56,58]	N-Sig: 1[56]	/		/	/
5. NFCS	2	N-Sig: 1[48]	Sig: 1[48] N-Sig: 1[56]	N-Sig: 1[56]	/	/	/	N-Sig: 1[48]
6. NIDCAP	2	/	N-Sig: 2[41,60]	/	/	/	/	/
7. Respiratory rate	2	/	N-Sig: 2[41,60]	/	/	/	/	/
8. COMFORT-b	2	/	Sig: 1[51] N-Sig: 1[56]	N-Sig: 1[56]	/	/	/	/
9. PIPP	1	N-Sig: 1[40]	N-Sig: 1[40]	N-Sig: 1[40]	/	/	/	/
10. ABC Pain Scale	1	/	Sig: 1[50]	/	/	/	/	/
11 N-PASS	1	N-Sig: 1[45]	N-Sig: 1[45]	N-Sig: 1[45]	/	/	/	/
12. BPSN	1	N-Sig: 1[59]	N-Sig: 1[59]	N-Sig: 1[59]	/	/	/	/
13. Crying time	1	N-Sig: 1[38]	Sig: 1[38]	Sig: 1[38]	/	/	/	/
B. Stimuli								
1. Phase of heel lance	10	Sig: 4[34,36,38,45] N-Sig: 2[39,59]	Sig: 9[34,36,38,39,42,45,46,51,56] N-Sig: 1[59]	Sig: 7[34,36,38,42,45,51,56] N-Sig: 2[39,59]	/	/	/	/
2. Phase of intubation	2	/	Sig: 2[52,57]	/	/	/	/	/
3. Phase of diaper change	2	N-Sig: 1[39]	Sig: 1[54] N-Sig: 1[39]	N-Sig: 1[39]	/	/	/	/
4. Phase of auditory stimuli	2	Sig: 1[37]	Sig: 2[37,41]	Sig: 1[37]	/	/	/	/
5. Type of procedure (heel lance vs. nursery handling)	2	/	Sig: 2[36,40]	Sig: 2[36,40]	/	/	/	/
6. Phase of pain stimuli (heel lance, venous blood sampling, intramuscular injections)	1	/	Sig: 1[58]	/	/	/	/	/
7. Phase of arterial blood sampling	1	/	Sig: 1[49]	/	/	/	/	/
8. Phase of venipuncture	1	/	Sig: 1[53]	/	/	/	/	/
9. Phase of airway suctioning	1	/	Sig: 1[49]	/	/	/	/	/
10. Phase of morning nursing care (axillary temperature, assessment, diaper change)	1	/	Sig: 1[60]	/	/	/	/	/
11. Phase of nursery handling	1	Sig: 1[36]	Sig: 1[36]	Sig: 1[36]	/	/	/	/
12. Phase of tactile stimuli (feeding+stethoscope)	1	N-Sig: 1[45]	N-Sig: 1[45]	N-Sig: 1[45]	/	/	/	/
13. Purpose of heel lance (glucose vs. blood sampling)	1	/	N-Sig: 1[46]	/	/	Sig: 1[46]	Sig: 1[46]	/
C. Age								
1. Gestational age	10	Sig: 2[19,36] N-Sig: 2[34,45]	Sig: 1[36] N-Sig: 8[34,42,43,45,46,51,55,56]	Sig: 1[36] N-Sig: 5[34,42,45,51,55]	N-Sig: 2[55,56]	N-Sig: 2[55,56]	N-Sig: 1[46]	/
2. Postnatal age	9	N-Sig: 4[34,36,37,45]	Sig: 1[34] N-Sig: 8[36,37,42,43,45,46,51,56]	Sig: 2[34,36] N-Sig: 6[36,37,42,45,51,56]	/	N-Sig: 1[46]	N-Sig: 1[46]	/
D. Other contextual variables								
1. Sex (male vs. female)	7	N-Sig: 3[37,40,59]	Sig: 2[41,46] N-Sig: 5[37,40,42,56,59]	N-Sig: 5[37,40,42,56,59]	/	N-Sig: 1[46]	N-Sig: 1[46]	/
2. Number of previous blood samplings	4	N-Sig: 1[34]	N-Sig: 4[34,51,56,58]	N-Sig: 2[51,56]	/	/	/	/
3. Delivery method	4	N-Sig: 2[37,40]	N-Sig: 4[37,40,42,56]	N-Sig: 4[37,40,42,56]	/	/	/	/
4. Oral sweet solution	3	N-Sig: 2[38,45]	N-Sig: 3[38,45,53]	/	/	/	/	/
5. Skin temperature	2	N-Sig: 1[37]	N-Sig: 2[37,47]	N-Sig: 1[37]	/	/	/	/
6. Current weight	2	/	N-Sig: 2[42,56]	N-Sig: 2[42,56]	/	/	/	/
7. Illness severity	1	/	N-Sig: 1[60]	/	/	/	/	/
8. Environment temperature	1	N-Sig: 1[39]	N-Sig: 1[39]	N-Sig: 1[39]	/	/	/	/
9. Skin-to-skin contact vs. cot	1	/	Sig: 1[54]	/	/	/	/	/
10. Gastroesophageal reflux	1	/	Sig: 1[44]	N-Sig: 1[44]	N-Sig: 1[44]	N-Sig: 1[44]	/	/
11. Neonatal abstinence system	1	N-Sig: 1[59]	Sig: 1[59]	N-Sig: 1[59]	/	/	/	/

/ indicates not studied; AHP, area huge peaks; AP, average peak; ART, average rise time; ASP, area small peaks; AUC, area under the curve; BPSN, Bernese Pain Scale For Neonates; COMFORT-b, Comfort Behavior Scale; N, number of studies; NFCS, Neonatal Facial Coding System; NIDCAP, Newborn Individualized Development Care and Assessment Program; NIPS, Neonatal Infant Pain Scale; N-PASS, Neonatal Pain Agitation and Sedation Scale; N-Sig, not statistically significant; NWps, number of waves per second; PIPP, Premature Infant Pain Profile; SC, skin conductance; SCL, mean skin conductance level; Sig, statistically significant.

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method,[37,40,42,56] administration of oral sweet solution before painful procedures,[38,45,53] skin temperature,[37,47] environmental temperature,[39] current weight,[42,56] number of previous blood sampling procedures,[34,51,56,58] and severity of illness.[60] However, skin-to-skin contact during painful procedures reduced NWps significantly compared with laying in incubators or cots.[54] Moreover, infants who had gastroesophageal reflux[44] and neonatal abstinence syndrome[59] had higher NWps than those who were healthy.

DISCUSSION

Given the absence of a gold standard for pain assessment in infants, and the inability of infants to report their pain verbally, physiological (eg, HR) indicators have been applied either alone or combined in a multidimensional pain instrument (eg, a pain scale including both behavioral and physiological indicators) to measure pain in infants.[3,16] The use of SC is a novel and emerging technique in infant acute pain and stress measurement.

This scoping review examined the use of SC for pain assessment in infants and demonstrated an increase in research using SC to assess acute pain in infants, with most of the studies being published in the last 10 years. The review also synthesized the literature on the validity of the SC among full-term and preterm infants within different clinical settings, identifying the validity evidence of SC in relation to 4 categories of variables: referent pain measures, stimuli, age, and other variables.

This scoping review showed inconsistent results of SC validity in the studies. Cohen et al[65] provided the criteria of "well-established assessment," which states "Detailed (eg, statistics presented) information indicating good validity in at least 1 peer-reviewed article." However, they did not clarify the standards of judging "well-established assessment" when the number of studies indicating poor psychometric properties is more than those indicating good properties. In addition, it was not possible to synthesize findings across the studies using meta-analyses due to wide variation in data collection procedures and analysis techniques being utilized in studies. Thus, recommendations for SC use in infant pain measurement could not be generated in this scoping review.

Relationships to Referent Pain Measures

SC was compared with various referent pain measures in the studies, as there is no clear gold standard for pain assessment in infants. SC was not significantly correlated with vital signs, except for HR in 2 of the 8 studies[38,41]; however, using HR as an indicator of the presence of pain in infants is not recommended,[18] because HR is influenced by multiple factors other than pain, including gestational age and postnatal age, severity of illness, hydration status, and pharmacological interventions (analgesics, and cardioactive and vasoactive drugs).[12] This could also explain why SC was significantly correlated with the unidimensional behavioral pain assessment scales (eg, NFCS,[48] COMFORT-b,[51] and ABC Pain Scale[50]) and crying time[53] rather than multidimensional indicators (including behaviors and vital signs or state of awareness, for example, NIPS,[53,56,58] PIPP,[40] N-PASS,[45] and BPSN[59]).

Prechtl Behavioral Scale[19,34,35,37,38,42,55,59] and NIDCAP[41,60] were used in a number of studies as referent behavioral measures. The Med-Storm Innovations User Manual recommended the cutoff point of the NWps to measure pain intensity compared with different behavioral states according to Prechtl Scale.[21] However, Prechtl Scale and NIDCAP did not show acceptable initial psychometric properties with respect to pain measurement in infants, as they were developed and validated to measure state of arousal and general movements.[65,66] Thus, the statistically significant findings could not support the validity evidence of SC measures for pain assessment in infants but could imply that the state of arousal and general movements is probably a covariate, which needs to be considered in further studies.[19,35,37,38,59]

Diagnostic test accuracy analysis provides more information on validity evidence than correlation or regression statistical methods.[67] Only 1 study reported the PPV and NPV of the SC.[48] The low PPV in the study indicated that many of the positive results from the SC measures are false positives, for example, 78.6% (NWps), 83.9% (Average Peak), and 84.8% (SCL) of the patients, respectively, could be overtreated.[48] Thus, it is necessary to follow-up any positive result with other pain measures having higher specificity to obtain a more accurate assessment as to whether pain is present. The strength of the SC measures test is instead in its high NPV, which, if negative for pain assessment in an infant, gives health care professionals a high confidence that its negative result is true, for example, only 5.6% (NWps), 1.8% (average peak), and 5.6% (SCL) of patients, respectively, could be undertreated in the study.[48]

Relationships to Stimuli

In the absence of a gold standard for pain assessment in infants, multiple approaches were used to validate the SC measures. One of the approaches is analyzing the SC changes before, during, and after painful or nonpainful procedures. Although 93.3% studies showed that SC increased significantly during painful procedures,[34,36,38,39,42,45,46,49,51–53,56,58] SC also increased significantly during nonpainful procedures in more than half of the studies.[36,37,41,54,60] As the biological mechanism of SC is based on how the sympathetic nervous system responds to stress, it is also expected that SC will increase during procedures that are stressful as well as procedures that are painful to infants. However, it is difficult to make a judgment about whether the SC values during nonpainful procedures indicate the presence of pain when these SC values were not compared with those collected during painful procedures.

In Pereira-da-Silva et al's[46] study, the SC parameters area small peaks and average rise time were significantly different when heel lance was used to draw blood for gas analysis compared with when it was used for glycemia. Larger area under the small peaks (bigger area small peaks value) and swifter SC rises (smaller average rise time value) indicate the sympathetic nervous system is firing more forcefully and suggest a more intense stimulus.[68] This could explain the finding in Pereira-da-Silva et al's[46] study, as heel lance for gas analysis requires collecting a larger volume of blood for a longer period than for glycemic testing. This finding may suggest that standardizing the specific type or process of the painful or nonpainful procedure is necessary in SC validation studies. However, it could be a common limitation in most of the included studies, as the standardization of procedures was not used.

Relationships to Age

In theory, the sympathetic nervous system becomes active in infants beyond 25 weeks of gestational age.[69] The statistically significant relationships between SC and

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gestational age[19,34] and postnatal age[34,36] were found in only 2 studies, respectively, accounting for <20% of the total articles studying validity evidence of SC in relation to gestational age[19,34,36,42,43,45,46,51,55,56] and postnatal age.[36,37,41,42,45–47,51,53] There remains a lack of strong evidence to support infants' naturally reactive SC responses being different across different age groups.[70] In addition, it is difficult to draw conclusions on the relationships of SC with gestational age or postnatal age, as not all the covariates were considered in the majority of studies, which is also suggested in the systematic review of cardiovascular indices (eg, heart rate change and heart rate variability) of acute pain responses in infants.[18]

Relationships to Other Contextual Variables

Validity evidence is not intrinsic to the measure but an interaction between the tool, the population to which it is applied, and the context under which it is applied.[29] Most of the context variables were not significantly related to SC, such as birth delivery methods, skin or environment temperature, current weight, and severity of illness. Pain treatments (eg, analgesics, skin-to-skin contact, and sweet solutions) are one of the most important contexts in SC validation studies, as they are supposed to decrease pain intensity and, therefore, SC values significantly. Skin-to-skin contact did lead to a significantly lower SC in infants during diaper change compared with laying in incubators or cots.[54] The effect of oral sucrose on SC compared with water was tested in 2 studies; however, no statistically significant relationships were found.[38,53] One of the reasons may have been due to the small sample sizes in the studies ($n = 12$[38,53] in sucrose group). However, no validity evidence of SC in relation to analgesics (eg, fentanyl, morphine) was evaluated in any included study. Thus, the ability of SC to detect changes in pain due to the pain treatments is one of the criteria of a validated pain assessment tool and needs to be studied further in the validation studies of SC for pain assessment in infants.[1]

Future Implications

The majority of studies included only healthy infants or infants with mild severity of illness, who were breathing spontaneously with no sedation or neuromuscular blockers; however, infants receiving invasive mechanical ventilation are one of the most vulnerable populations. First, mechanical ventilation is associated with high numbers of stressful and painful procedures required during ongoing mechanical ventilation and medical and nursing care.[71] Second, infants receiving mechanical ventilation are critically ill and sensitive to suboptimal analgesia.[72,73] Lastly, ventilated infants sometimes receive sedatives or muscle relaxants, which can lead to altered pain responses compared with other groups of infants.[12] The airway tube, tube holder, and tape over the infants' lower half of the face (mouth and lips) may limit clinicians' view and subsequent accurate assessment of their facial expressions of pain.[10] Thus, this is a patient population that investigators should study to ascertain whether SC is useful, feasible, and a validated physiological indicator to assess stress and pain in infants.

Although the emerging SC validation literature provides some evidence with regard to use as an infant pain and stress assessment measure, there are several common limitations of the studies that warrant consideration. First, the majority of studies examining SC as a pain measurement in infants used the device from Med-Storm Innovations (owned by Dr Storm).[34–58,60] Although this replication provided consistent evidence, only a few studies reported the mechanism and quality of the device from Med-Storm Innovations to measure SC, which could introduce test bias in studies.[74] Second, the quality of data collection using the SC measurement device needs to be considered in future studies. Although not all the studies reported missing data, 12 of 28 included studies reported reasons for missing data, which showed that, in nearly 10% of the infants studied, there were technical issues of the SC measurement device or electrodes when using the SC measurement device to detect pain.[37,39,40,42–44,48,52,54,56,57,59] Lastly, the method of analyzing and choosing SC values to represent pain intensity in a specific period of time is unclear in most studies. Only Lyngstad et al's[54] study reported that they used maximum SC values. Different methods of analysis and choice (mean, median, or maximum) of SC values probably change the findings in the studies, as SC values are continuous variables and change rapidly during the measurement.

Strengths and Limitations

To our knowledge, this is the first scoping review examining the use of SC for pain assessment in infants. The strengths of this study lie in the involvement of a multifaceted approach to identify relevant validity evidence of SC for pain assessment in infants and the inclusion of different types of studies, which together increased the comprehensiveness of the validity evidence. However, this review had several limitations. First, it was restricted to studies published in English. Second, frequencies rather than further syntheses were used in this review to describe the evidence due to heterogeneous study designs. Finally, the weight of evidence and recommendations were not analyzed, as there were no appropriate standards available to demonstrate whether the evidence is sufficient to support the validity evidence of SC.

CONCLUSIONS

This scoping review identified emerging literature on validity evidence of SC for pain assessment in infants in relation to referent pain measures, stimulus, age, and other contextual variables. The descriptions of the validity evidence of SC for assessing acute pain in infants in the literature and how the validation studies were conducted demonstrated that SC may be a promising pain measurement in infants. However, the inconsistent findings in the studies suggest that further research is needed before it could be applied to the clinical settings. Future research should aim to identify the diagnostic test accuracy of SC compared with well-accepted referent pain measures in infants, study the validity evidence of SC in a specific population (eg, infants receiving mechanical ventilation, sedation, or neuromuscular blockers), and use rigorous research design and transparent reporting. Finally, it is imperative to keep in mind that SC is only 1 indicator of infants' response to pain and should be considered with other sources of information, including behavioral indicators and context, on the presence of pain.

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Supplemental Digital Content 1. Skin Conductance Parameters Definition

SC parameters	Definition
Mean skin conductance level	The value of skin conductance activity
Number of waves per second[2]	This is the number of peaks in the window divided by the time span of the window.
Area under curve	In some situations, it is valuable to look at the larger of the two measures "Area huge peaks" and "Area small peaks". This is then referred to as "Area under curve".
Area huge peaks	This measure is calculated by establishing a horizontal base line from the first peak minimum in the time window. The area that is calculated is the accumulated difference between the conductance values at the registration curve and the established baseline when they are larger than the baseline.
Area small peaks	This measure is calculated by establishing a line between two adjacent peak minimum points. The area is the accumulated difference between the line and the skin conductance registration curve values when they are larger than the line.
Average Rise Time	This measure is the rate of increase or decrease from the start to the end of the measurement window.
Average Peak	The difference in conductance value between the identified maximum and minimum of one peak is its peak value. The average is calculated from all peaks in the time window.

Note:

1. Med-Storm Innovation AS. (2012). Med-Storm Pain Monitor User Manual. Retrieved November 11th, 2016, from http://www.med-storm.com/pdf/UserManualEnglsihMA00127_20130424.pdf

2. Number of Waves per second is also referred to as Number of Peaks per second in literature.

Supplemental Digital Content 2. Scoping Review Search Strategy

EBSCO CINAHL

S14 S12 AND S13

S13 S6 OR S7 OR S8 OR S9 OR S10 OR S11

S12 S1 OR S2 OR S3 OR S4 OR S5

S11 TI nocicept* OR AB nocicept*

S10 TI stress* OR AB stress*

S9 TI pain* OR AB pain*

S8 (MH "Pain") OR (MH "Pain Measurement") OR (MH "Pain Threshold")

S7 (MH "Nociceptive Pain")

S6 (MH "Stress") OR (MH "Stress Management")

S5 TI (Galvanic W2 (conduct* OR response* OR resistan*)) OR AB (Galvanic W2 (conduct* OR response* OR resistan*))

S4 TI (cutaneous W2 (conduct* OR response* OR resistan*)) OR AB (cutaneous W2 (conduct* OR response* OR resistan*))

S3 TI (electrodermal W2 (conduct* OR response* OR resistan*)) OR AB (electrodermal W2 (conduct* OR response* OR resistan*))

S2 TI (skin W2 (conduct* OR response* OR resistan*)) OR AB (skin W2 (conduct* OR response* OR resistan*))

S1 (MH "Skin")

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1. Galvanic Skin Response/

2. (cutaneous adj2 (conduct* or response* or resistan*)).ti,ab.

3. (skin adj2 (conduct* or response* or resistan*)).ti,ab.

4. (electrodermal adj2 (conduct* or response* or resistan*)).ti,ab.

5. (Galvanic adj2 (conduct* or response* or resistan*)).ti,ab.

6. Pain Perception/ or Pain Threshold/ or Pain Insensitivity, Congenital/ or Pain Measurement/ or Pain/ or Nociceptive Pain/ or Pain Management/

7. pain*.ti,ab.

8. Stress, Psychological/ or Stress, Physiological/

9. stress*.ti,ab.

10. Nociception/

11. nocicept*.ti,ab.

12. 1 or 2 or 3 or 4 or 5

13. 6 or 7 or 8 or 9 or 10 or 11

14. 12 and 13

OVID Embase 1974 to 2016 October 11

Search:
1. skin conductance/ or electrodermal response/
2. (cutaneous adj2 (conduct* or response* or resistan*)).ti,ab.
3. (skin adj2 (conduct* or response* or resistan*)).ti,ab.
4. (electrodermal adj2 (conduct* or response* or resistan*)).ti,ab.
5. (Galvanic adj2 (conduct* or response* or resistan*)).ti,ab.
6. pain threshold/ or pain intensity/ or pain measurement/ or pain severity/ or pain parameters/ or pain/ or nociceptive pain/ or pain assessment/
7. nociception/
8. physically induced stress/ or physical stress/ or physiological stress/ or stress/ or stress assessment/
9. pain*.ti,ab.
10. nocicept*.ti,ab.
11. stress*.ti,ab.
12. 1 or 2 or 3 or 4 or 5
13. 6 or 7 or 8 or 9 or 10 or 11
14. 12 and 13

OVID PsycINFO 1806 to October Week 1 2016
1. Skin Resistance/ or Galvanic Skin Response/
2. (cutaneous adj2 (conduct* or response* or resistan*)).ti,ab.
3. (skin adj2 (conduct* or response* or resistan*)).ti,ab.
4. (electrodermal adj2 (conduct* or response* or resistan*)).ti,ab.
5. (Galvanic adj2 (conduct* or response* or resistan*)).ti,ab.
6. Pain Management/ or Pain Perception/ or Pain Measurement/ or Pain Thresholds/ or Pain/
7. Physiological Stress/ or Psychological Stress/ or Stress Management/ or Stress/ or Stress Reactions/
8. pain*.ti,ab.
9. nocicept*.ti,ab.
10. stress*.ti,ab.
11. 1 or 2 or 3 or 4 or 5
12. 6 or 7 or 8 or 9 or 10
13. 11 and 12

Other Resources

ProQuest Dissertations & Theses Global

Search: (ti(pain*) OR ab(pain*) OR ti(stress*) OR ab(stress*) OR ti(nocicept*) OR ab(nocicept*)) AND ((ti(skin PRE/2 (conduct* OR response* OR resistance*)) OR ab(skin PRE/2 (conduct* OR response* OR resistance*))) OR (ti(electrodermal PRE/2 (conduct* OR response* OR resistance*)) OR ab(electrodermal PRE/2 (conduct* OR response* OR

resistance*))) OR (ti(cutaneous PRE/2 (conduct* OR response* OR resistance*)) OR ab(cutaneous PRE/2 (conduct* OR response* OR resistance*))) OR (ti(Galvanic PRE/2 (conduct* OR response* OR resistance*)) OR ab(Galvanic PRE/2 (conduct* OR response* OR resistance*))))

ClinicalTrials.gov (www.clinicaltrials.gov)
metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct)
World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/)
Search:
skin conduct* | "Pain"
skin response* | "Pain"
skin resistance* | "Pain"
electrodermal conduct* | "Pain"
electrodermal response* | "Pain"
cutaneous response* | "Pain"
cutaneous conduct* | "Pain"
Galvanic conduct* | "Pain"
Galvanic response* | "Pain"

Supplemental Digital Content 3. Exclusion List by Reason (N=166)

Citation	Exclusion reason
Volf N, Ferdman L. Auricular Causative Diagnosis - Finding the Roots of Diseases: A Study of Clinical Cases United States: Mary Ann Liebert Inc. (E-mail: info@liebertpub.com); 2016 [cited 28]. (Volf, Ferdman) Scientific Acupuncture Diploma of the Medical Faculty of Paris XI University, 9 rue Quentin Bauchart, Paris 75008, France:[206-16].	Not using SC
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Bergmann I, Hesjedal B, Crozier TA, Poschl R, Bauer M, Hinz JM, Buttner B. Selective unilateral spinal anaesthesia for outpatient knee arthroscopy using real-time monitoring of lower limb sympathetic tone Australia: Australian Society of Anaesthetists (E-mail: AIC@ASA.ORG.AU); 2015 [cited 43]. (Bergmann, Hesjedal, Crozier, Bauer, Hinz, Buttner) Department of Anaesthesiology, Emergency and Intensive Care Medicine, University of Gottingen Medical School, Gottingen, Germany:[351-6].	Not using SC
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Supplemental Digital Content 4. Detailed Description of Validity Evidence of SC

A. Pain measures

1. Heart rate

Storm, 2002	[NWps] Significant: Simple linear regression analysis p=0.000, r2=0.417 [AUC] Significant: Simple linear regression analysis p=0.001, r2=0.205 [SCL] Significant: Simple linear regression analysis p=0.014, r2=0.137
Salavitabar, 2010	[NWps] Significant: Pearson correlation p=0.017, r=0.697
de Jesus, 2011	[NWps, AUC] Not Significant: Spearman correlation p>0.05
Roeggen, 2011	[NWps] Not Significant: Spearman correlation p>0.05
Lyngstad, 2014	[NWps] Not Significant: Spearman correlation p>0.05
Macko, 2014	[NWps, AUC, AHP, ASP] Not Significant: Simple linear regression analysis p>0.05
Gokulu,2016	[NWps] Not Significant: Spearman correlation p>0.05
Zeiner, 2016	[NWps] Not Significant: Spearman correlation p>0.05

2. Prechtl's scale

Gladman, 1990	[SCL] Significant (40-43 weeks GA): Mann-Whitney U test p<0.03, Awake 2-4 (1.2μS)>Asleep 0-1 (0.5μS)
Storm, 2000	[SCL, NWps, AUC] Not Significant: Spearman correlation p>0.05
Storm, 2001	[SCL] Significant (>=34 weeks GA): Wilcoxon signed-rank test p<0.05 Awake 2-4>Asleep 0-1 [NWps, AUC] Significant (>=29 weeks GA): Wilcoxon signed-rank test p<0.05 Awake 2-4>Asleep 0-1
Hernes, 2002	[SCL, NWps, AUC] Significant: Spearman correlation p<0.001

Storm, 2002	[NWps] Significant: Simple linear regression analysis p=0.003, r2=0.175 [AUC] Significant: Simple linear regression analysis p=0.045, r2=0.086 [SCL] Significant: Simple linear regression analysis p=0.003, r2=0.066
de Jesus, 2011	[NWps, AUC] Not Significant: Mann-Whitney U test p>0.05
Macko, 2014	[NWps, AUC, AHP, ASP] Not Significant: Simple linear regression analysis p>0.05
Schubach, 2016	[NWps, AUC, SCL] Significant: Mann-Whitney U test p<0.001, Awake2-4>Asleep0-1

3. Oxygen saturation

Salavitabar, 2010	[NWps] Not Significant: Pearson correlation p>0.05, r=0.328
de Jesus, 2011	[NWps, AUC] Not Significant: Spearman correlation p>0.05
Roeggen, 2011	[NWps] Not Significant: Spearman correlation p>0.05
Lyngstad, 2014	[NWps] Not Significant: Spearman correlation p>0.05
Macko, 2014	[NWps, AUC, AHP, ASP] Not Significant: Simple linear regression analysis p>0.05
Gokulu,2016	[NWps] Not Significant: Spearman correlation p>0.05

4. Neonatal Infant Pain Scale

Beken, 2014	[NWps] Not Significant: Spearman correlation p>0.05
de Jesus, 2015	[NWps, AUC] Not Significant: Spearman correlation p>0.05
Gokulu,2016	[NWps] Not Significant: Spearman correlation p>0.05

5. Neonatal Facial Coding System (NFCS)

Dalal, 2013	[SCL, AP] Not Significant: Kendall's rank correlation p>0.05 [NWps] Significant: Kendall's rank correlation p=0.006, tau-b=-0.4l **[**NWps]

	Area under the ROC curve: AUC 0.664 (0.514-0.813), Cut-off value 0.571 (NFCS≥4, moderate to severe pain), Sensitivity 54.5%, Specificity 79.4%, Positive predictive value 21.4%, Negative predictive value 94.4% [AP] Area under the ROC curve: AUC 0.6 (0.503-0.792), Cut-off value 0.042(NFCS≥4, moderate to severe pain), Sensitivity 90.9%, Specificity 51.4%, Positive predictive value 16.1%, Negative predictive value 98.2% [SCL] Area under the ROC curve: AUC 0.615 (0.435-0.795), Cut-off value 16.8 (NFCS≥4, moderate to severe pain), Sensitivity 63.6%, Specificity 63.5%, Positive predictive value 15.2%, Negative predictive value 94.4%
de Jesus, 2015	[NWps, AUC] Not Significant: Spearman correlation p>0.05

6. Newborn Individualized Developmental Care and Assessment Program

Salavitabar, 2010	[NWps] Not Significant: Pearson correlation p>0.05
Zeiner, 2016	[NWps] Not Significant: Spearman correlation p>0.05

7. Respiratory rate

Salavitabar, 2010	[NWps] Not Significant: Pearson correlation p>0.05, r=0.325
Zeiner, 2016	[NWps] Not Significant: Spearman correlation p>0.05

8. COMFORT-behavior (COMFORT-b)

Tristao, 2013	[NWps 15s] Significant: Spearman's correlation p<0.01, r=0.424 (COMFORT-B); p<0.01, r=0.576 (Alertness); p<0.01, r=0.449 (Calmness); p<0.05, r=0.328 (Crying); p<0.01, r=0.560 (Physical Movement); p<0.05, r=0.383 (Muscle Tone); p<0.01, r=0.418 (Facial Tension); Kendall's coefficient of concordance: p=0.023, tau-b=-0.303 (Facial Tension) [NWps 30s] Significant: Spearman's correlation p<0.05, r=0.383 (COMFORT-B); p<0.01, r=0.468 (Alertness); p<0.01, r=0.405 (Calmness); p<0.05, r=0.348 (Crying); p<0.01, r=0.533 (Physical Movement); p<0.05, r=0.404 (Muscle Tone); p<0.05, r=0.391 (Facial Tension) Not Significant: Kendall's coefficient of concordance [NWps 180s] Significant: Spearman's correlation p<0.01, r=0.504 (COMFORT-B);

	p<0.01, r=0.444 (Alertness); p<0.05, r=0.333 (Calmness); p<0.01, r=0.437 (Crying); p<0.01, r=0.609 (Physical Movement); p<0.01, r=0.413 (Muscle Tone); p<0.01, r=0.417 (Facial Tension); Kendall's coefficient of concordance p=0.006, tau-b=0.313 (COMFORT-B); p=0.001, tau-b=0.363 (Facial Tension); p=0.021, tau-b=0.270 (Muscular tone); p=0.006, tau-b=0.299 (Physical Movement); p=0.002, tau-b=0.321 (Alertness) [AUC 15s] Significant: Spearman's correlation p<0.01, r=0.431 (Alertness); p<0.05, r=0.316 (Calmness); p<0.01, r=0.424 (Physical Movement); p<0.05, r=0.327 (Facial Tension) [AUC 30s] Significant: Spearman's correlation p<0.05, r=0.314 (Physical Movement)
de Jesus, 2015	[NWps, AUC] Not Significant: Spearman correlation p>0.05

9. Premature Infant Pain Profile (PIPP)

Eriksson, 2008	[SCL, NWps, AUC] Not Significant: Spearman correlation p>0.05

10. ABC scale

Scaramuzzo, 2013	[NWps] Significant: Spearman correlation p<0.005, r=0.303

11. Neonatal Pain, Agitation and Sedation Scale

Munsters, 2012	[SCL, NWps, AUC] Not Significant: Spearman correlation p>0.05

12. Bernese Pain Scale for Neonates

Schubach, 2016	[NWps, AUC, SCL] Not Significant: Pearson correlation p>0.05

13. Crying time

Storm, 2002	[NWps] Significant: Simple linear regression analysis p=0.001, r2=0.427 [AUC] Significant: Simple linear regression analysis p=0.002, r2=0.196 [SCL] Not Significant: Simple linear regression analysis p=0.175, r2=0.044

B. Stimuli

1. Phase of heel lance

Storm, 2000	**Phase of heel lance for blood sampling** [SCL]

	Significant: Friedman test p<0.001, before (1.3, 0.6-4.4), during (1.7, 0.7-4.7)*, after (1.7, 0.7-5.8)* [NWps] Significant: Friedman test p<0.001, before (0, 0-0.2), during (0.03, 0-0.35)*, after (0, 0-0.26) [AUC] Significant: Friedman test p=0.001, before (0, 0-0.04), during (0.03, 0-0.07)*, after (0, 0-0.06)
Hellerud, 2002	**Phase of heel lance for blood sampling** [NWps] Significant (Newborn Preterm 29-35w): Wilcoxon Signed Ranks Test p<0.02, before (0.00), during (0.03) [SCL] Significant (Newborn Preterm 29-35w): Wilcoxon Signed Ranks Test p<0.02, before (1.20mS), during (1.60mS) [NWps] Significant (Postnatal Preterm 29-35w): Wilcoxon Signed Ranks Test p<0.02, before (0.01), during (0.08) [AUC] Significant (Postnatal Preterm 29-35w): Wilcoxon Signed Ranks Test p<0.02, before (0.02mS), during (0.04mS) [SCL] Significant (Postnatal Preterm 29-35w): Wilcoxon Signed Ranks Test p<0.02, before (1.80mS), during (2.40mS) [NWps] Significant (Newborn Full-term 39-43w): Wilcoxon Signed Ranks Test p<0.05, before (0.22), during (0.25) [AUC] Significant (Newborn Full-term 39-43w): Wilcoxon Signed Ranks Test p<0.05, before (0.09mS), during (0.13mS) [AUC] Significant (Postnatal Full-term 39-43w): Wilcoxon Signed Ranks Test p<0.05, before (0.16mS), during (0.23mS)
Storm, 2002	**Phase of heel lance for blood sampling** [SCL, NWps, AUC] Significant: Wilcoxon Signed Ranks Test p<0.05, Before<During
Harrison, 2006	**Phase of heel lance for blood sampling** [SCL, AUC]

	Not Significant: Paired t test p>0.05 [NWps] Significant: Paired t test p<0.05, During>Before
de Jesus, 2011	**Phase of heel lance for glucose test (Oberlander's Model)** [NWps] Significant (Intensity): Friedman test X2=13.07, p=0.001, before 0.12 (0-0.36), during 0.24 (0-0.6), after 0.13 (0-0.56) Significant (Reactivity & Direction, during-before): Wilcoxon Signed Ranks Test Z=-4.20, p=0.000, 0.12 (-0.2 – 0.53) Significant (Regulation & Direction, after-during): Wilcoxon Signed Ranks Test Z=-3.48, p=0.000, -0.11 (-0.6-0.23) [AUC] Significant: Friedman test X2=7.02, p=0.03, before 1.43μS (0-6.45), during 1.85μS (0-9.77), after 1.10μS (0-10.91) Significant (Regulation & Direction, after-during): Wilcoxon Signed Ranks Test Z=-2.36, p=0.042 -0.74 (-9.77 -8.07)
Munsters, 2012	**Phase of heel lance for blood sampling** [SCL, NWps, AUC] Significant: Repeated-measures ANOVA p<0.05
Pereira-da-Silva, 2012	**Phase of heel lance for blood sampling or glucose test** [NWps] Significant: Wilcoxon Signed Ranks Test p<0.001
Tristao, 2013	**Phase of heel lance for glucose test** [NWps] Significant: Mann-Whitney U Test p<0.01 During-Before Mean 0.12 (Range -0.2-0.53); p<0.01 During-After Mean 0.11 (Range -0.86-0.4) [AUC] Significant: Mann-Whitney U Test p<0.05 During-After Mean 0.74 (Range -9.77-8.07)
de Jesus, 2015	**Phase of heel lance for glucose test** [NWps] Significant: Friedman test p=0.001, X2=13.07, Before (Mean0.12, Range 0-0.36) During (Mean0.24, Range0-0.6), After (Mean0.13, Range0-0.56) Significant: Wilcoxon Signed Ranks Test p<0.01 Difference between during and before (Mean0.12, Range -0.2 to 0.53), Difference between after and during (Mean-0.11, Range -0.6 to 0.23) [AUC] Significant: Friedman test p=0.03, X2=7.02, Before (Mean1.43, Range 0-

	6.45) During (Mean1.85, Range0-9.77), After (Mean1.10, Range0-10.91) Significant: Wilcoxon Signed Ranks Test p<0.05 Difference between after and during (Mean-0.74, Range -9.77 to 8.07)
Schubach, 2016	**Phase of heel lance for blood sampling** [NWps] Not Significant: Wilcoxon Signed Ranks Test Neonatal Abstinence System p=0.48; Non-Substance-Exposed p=0.08 [AUC] Not Significant: Wilcoxon Signed Ranks Test Neonatal Abstinence System p=0.80; Non-Substance-Exposed p=0.08 [SCL] Not Significant: Wilcoxon Signed Ranks Test Neonatal Abstinence System p=0.05; Non-Substance-Exposed p=0.45

2. Phase of intubation

Baleine, 2014	**Phase of intubation with nasal midazolam** [NWps] Significant: Repeated-measures ANOVA p=0.044, before 0.07 (0-0.13), after 0.13 (0.07-0.27)
van der Lee, 2015	**Phase of intubation** [NWps] Descriptive statistics: Administration of morphine (0.1mg/kg, range 1.4–10.3 min) before administration of vecuronium did not affect SC when a stressful stimulus was applied. Within 1.6 min (2mg/kg, range 0.8-3 min) after administration of vecuronium (0.1mg/kg), SC disappeared in 10 of 11 newborns (median 0, range 0-0.27). Propofol reduced SC in 10 of 11 newborns at the first attempt (median 0.04, range 0.00-0.33). Further attempts were associated with increasing SC, mostly above a threshold of 0.21 peaks/s.

3. Phase of diaper change

Harrison, 2006	[SCL, AUC] Not Significant: Paired t test p>0.05 [NWps] Significant: Paired t test p<0.05, After<Before
Lyngstad, 2014	[NWps] Significant: Paired t tests p<0.05, During>Before

4. Phase of auditory stimuli

Hernes, 2002	[SCL, NWps, AUC] Significant: One-way ANOVA p<0.05

Salavitabar, 2010	[NWps] Significant: Paired t test p<0.001, Baseline sound stimuli (<55dBA) <High sound stimuli (>65dBA)

5. Type of procedure

Hellerud, 2002	**Heel lance for blood sampling vs. Nursery handling** [SCL, NWps, AUC] Significant (Newborn Preterm 29-35w): Mann-Whitney U Test p<0.05, Heel Lance for blood sampling> Nursery Handling
Eriksson, 2008	**Heel lance for blood sampling vs. Nursery handling** [SCL] Not Significant: Mann-Whitney U Test p>0.05, Changes before and during tactile stimulation 0.01(-0.04 to 0.18) = Changes before and during heel lance 0.14(-0.02 to 0.54) [AUC] Significant: Mann-Whitney U Test p=0.006, Changes before and during tactile stimulation 0.00(-0.02 to 0.02) = Changes before and during heel lance 0.03 (-0.02 to 0.04) [NWps] Significant: Mann-Whitney U Test p=0.026, Changes before and during tactile stimulation 0.03(-0.08 to 0.07) < Changes before and during heel lance 0.08 (0.03 to 0.20)

6. Phase of pain stimuli (heel lance, venous blood sampling, intramuscular injections)

Gokulu,2016	[NWps] Significant: Wilcoxon Signed Ranks Test p<0.001, Before (Receiving at least five painful procedures, 0-30s) Median 0.00 (Range 0.00-0.20), During (Receiving at least five painful procedures, 0-30s) Median 0.23 (Range 0.09-0.50); Before (Receiving at least five painful procedures, 0-45s) Median 0.00 (Range 0.00-0.20), During (Receiving at least five painful procedures, 0-45s) Median 0.27 (Range 0.08-0.58); Before (Receiving vitamin K and hepatitis B injections, 0-30s) Median 0.00 (Range 0.00-0.30), During (Receiving vitamin K and hepatitis B injections, 0-30s) Median 0.27 (Range 0.05-0.50); Before (Receiving vitamin K and hepatitis B injections, 0-45s) Median 0.00 (Range 0.00-0.30), During (Receiving vitamin K and hepatitis B injections, 0-45s) Median 0.27 (Range 0.06-0.43)

7. Phase of arterial blood sampling

Karpe, 2013	[NWps] Significant: One-way ANOVA and post-hoc Tukey HSD test p<0.001,

	baseline 0.20 (0.18-0.23), arterial blood sampling 0.35 (0.33-0.37) Significant: X2 test P<0.001 percentage of NWps>0.14 baseline 27.85%, arterial blood sampling 59.70%; X2 test p<0.001 percentage of NWps>0.33 baseline 19.18%, arterial blood sampling 38.63%

8. Phase of venipuncture

Beken, 2014	[NWps] Significant: Wilcoxon Signed Ranks Test p=0.002 Sucrose during 0.37 (0.03-0.90), Sucrose after 0.03 (0.0-0.20); p=0.006 Pacifier during 0.37 (0.1-0.90), Pacifier after 0.03 (0.0-0.60)

9. Phase of airway suctioning

Karpe, 2013	[NWps] Significant: One-way ANOVA and post-hoc Tukey HSD test p<0.001, baseline 0.20 (0.18-0.23), airway suctioning 0.33 (0.31-0.36) Significant: X2 test P<0.001 percentage of NWps>0.14 baseline 27.85%, airway suctioning 59.94%; X2 test p<0.001 percentage of NWps>0.33 baseline 19.18%, airway suctioning 35.91%

10. Phase of morning nursing care (axillary temperature, assessment, diaper change)

Zeiner, 2016	[NWps] Significant: Wilcoxon Signed Ranks Test p<0.0001, Before (Mean 0.06, SE 0.009), After (Mean 0.13, SE 0.014)

11. Phase of nursery handling

Hellerud, 2002	[NWps] Significant (Newborn Preterm 29-35w): Wilcoxon Signed Ranks Test p<0.02, before (0.03), during (0.20) [AUC] Significant (Newborn Preterm 29-35w): Wilcoxon Signed Ranks Test p<0.02, before (0.02mS), during (0.06mS) [SCL] Significant (Newborn Preterm 29-35w): Wilcoxon Signed Ranks Test p<0.02, before (1.20mS), during (1.69mS) [NWps] Significant (Postnatal Preterm 29-35w): Wilcoxon Signed Ranks Test p<0.02, before (0.01), during (0.19) [AUC] Significant (Postnatal Preterm 29-35w): Wilcoxon Signed Ranks Test p<0.02, before (0.01mS), during (0.06mS) [SCL] Significant (Postnatal Preterm 29-35w): Wilcoxon Signed Ranks Test

	p<0.02, before (2.00mS), during (3.22mS) [NWps] Significant (Newborn Full-term 39-43w): Wilcoxon Signed Ranks Test p<0.05, before (0.35), during (0.72) [AUC] Significant (Newborn Full-term 39-43w): Wilcoxon Signed Ranks Test p<0.05, before (0.11mS), during (0.22mS)

12. Phase of tactile stimuli (Feeding, Cold or warm stethoscope)

Munsters, 2012	[SCL, NWps, AUC] Not Significant: Repeated-measures ANOVA p>0.05

13. Purpose of heel lance (blood being drawn for blood gas analysis compared to for glycaemia)

Pereira-da-Silva, 2012	[NWps] Not Significant: Mann-Whitney U Test p>0.05 [ASP] Significant: Mann-Whitney U Test p=0.001 [ART] Significant: Mann-Whitney U Test p=0.037

C. Age

1. Gestational age

Gladman, 1990	[SCL] Significant: Mann-Whitney U Test p<0.01, 28-39 weeks (0.3μS)<40-43weeks (0.6μS)
Storm, 2000	[SCL, NWps, AUC] Not Significant: Spearman correlation p>0.05
Hellerud, 2002	[SCL] Significant (Postnatal, During Heel Lance): Mann-Whitney U Test p=0.001, Preterm>Full-term [NWps, AUC] Significant (Postnatal, During Nursery Handling): Mann-Whitney U Test p<0.05, Preterm<Full-term
de Jesus, 2011	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA p>0.05
Roeggen, 2011	[NWps] Not Significant: Simple linear regression analysis p>0.05
Munsters, 2012	[SCL, NWps, AUC] Not Significant: Independent sample t test p>0.05, <28 weeks GA=>28 weeks GA

Pereira-da-Silva, 2012	[NWps, ASP, ART] Not Significant: Multivariate logistic regression analysis p>0.05
Tristao, 2013	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA p>0.05
Macko, 2014	[NWps, AUC, AHP, ASP] Not Significant: Simple linear regression analysis p>0.05
de Jesus, 2015	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA p>0.05

2. Postnatal age

Storm, 2000	[NWps] Significant: Simple linear regression analysis p=0.01, r2=0.29 [AUC] Significant: Simple linear regression analysis p=0.004, r2=0.357 [SCL] Not Significant: Simple linear regression analysis p>0.05
Hellerud, 2002	[SCL, NWps] Not Significant (Preterm 29-35w): Mann-Whitney U test p>0.05 [AUC] Significant (Fullterm 39-43w, During Nursery Handling): Mann-Whitney U test p<0.01, Postnatal <Newborn [SCL, NWps] Not Significant (Fullterm 39-43w, During Nursery Handling): Mann-Whitney U test p>0.05 [SCL, NWps] Not Significant (Fullterm 39-43w, During Heel Lance): Mann-Whitney U test p>0.05
Hernes, 2002	[SCL, NWps, AUC] Not Significant: Multivariable analysis p>0.05
de Jesus, 2011	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA analysis p>0.05
Roeggen, 2011	[NWps] Not Significant: Simple linear regression analysis p>0.05
Munsters, 2012	[SCL, NWps, AUC] Not Significant: Independent sample t test p>0.05, <28 days PNA=>28 days PNA
Pereira-da-Silva, 2012	[NWps, ASP, ART] Not Significant: Multivariate logistic regression analysis p>0.05

Tristao, 2013	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA p>0.05
de Jesus, 2015	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA p>0.05

D. Other contextual variables

1. Sex

Hernes, 2002	[SCL, NWps, AUC] Not Significant: Multivariable Analysis p>0.05
Eriksson, 2008	[SCL, NWps, AUC] Not Significant: Mann-Whitney U test p>0.05
Salavitabar, 2010	[NWps] Significant: Independent samples *t* tests p=0.03, Male>Female
de Jesus, 2011	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA analysis p>0.05
Pereira-da-Silva, 2012	[NWps] Significant: Multivariate logistic regression analysis p=0.004, Female>Male [ASP, ART] Not Significant: Multivariate logistic regression analysis p>0.05
de Jesus, 2015	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA p>0.05
Schubach, 2016	[NWps, AUC, SCL] Not Significant: Multilevel longitudinal models p>0.05

2. Number of previous blood sampling

Storm, 2000	[NWps] Not Significant (During heel lance): Simple linear regression analysis p=0.05, r2=0.18 [SCL] Not Significant (During heel lance): Simple linear regression analysis p>0.05
Tristao, 2013	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA p>0.05
de Jesus, 2015	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA p>0.05
Gokulu,2016	[NWps] Not Significant: Mann-Whitney U test p=0.754, Receiving at least five painful procedures=Receiving vitamin K and hepatitis B injections

3. Delivery method

Hernes, 2002	[SCL, NWps, AUC] Not Significant: Multivariable Analysis p>0.05
Eriksson, 2008	[SCL, NWps, AUC] Not Significant: Mann-Whitney U test p>0.05
de Jesus, 2011	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA analysis p>0.05
de Jesus, 2015	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA analysis p>0.05

4. Oral sweet solution

Storm, 2002	[SCL, NWps, AUC] Not Significan: Wilcoxon Signed Ranks Test p>0.05
Munsters, 2012	[SCL, NWps, AUC] Not Significant: Repeated-measures ANOVA p>0.05
Beken, 2014	[NWps] Not Significant: Wilcoxon Signed Ranks Test p>0.05

5. Skin temperature

Hernes, 2002	[SCL, NWps, AUC] Not Significant: Multivariable Analysis p>0.05
Valkenburg, 2012	[NWps] Not Significant: Spearman correlation p<0.001

6. Current weight

de Jesus, 2011	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA p>0.05
de Jesus, 2015	[NWps, AUC] Not Significant: Generalized Linear Model Two-way ANCOVA p>0.05

7. Severity of illness score (Score for neonatal acute physiology)

Zeiner, 2016	[NWps] Not Significant: Pearson Correlation p>0.05

8. Environment temperature

Harrison, 2006	[SCL, NWps, AUC] Not Significant: One-way ANOVA p>0.05 (Open Cot, Incubator, Radiant Heater)

9. Skin-to-skin contact

Lyngstad, 2014	[NWps] Significant: Paired t test p=0.028, mean paired difference -0.089 (95% CI -

	0.168 to- 0.011)

10. Gastroesophageal reflux

Cresi, 2012	[NWps] Significant: Mann-Whitney U test $p<0.05$ [AUC, AHP, ASP] Not Significant: Mann-Whitney U test $p>0.05$

11. Neonatal abstinence syndrome (NAS)

Schubach, 2016	[NWps] Significant: Multilevel longitudinal models p=0.04, Neonatal Abstinence System>Non-Substance-Exposed 49% (95% CI 9%-104%) [AUC] Not Significant: Multilevel longitudinal models $p>0.05$ **Finnegan score (Neonatal abstinence system)** [NWps] Not Significant: Pearson Correlation p=0.39 [AUC] Not Significant: Pearson Correlation p=0.39 [SCL] Not Significant: Pearson Correlation p=0.41

Chapter 3: Manuscript Two. The Validity of Skin Conductance for Measuring Pain in Mechanically Ventilated Infants

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Title Page

The Validity of Skin Conductance for Measuring Pain in Mechanically Ventilated Infants

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1. Introduction

Despite significant advances in the knowledge of pain in infants, poorly managed pain in this population remains a problematic issue across different settings, especially for sick hospitalized infants.[37] Infants requiring respiratory support by mechanical ventilation are one of the most vulnerable populations, due to the critical nature of the illness, invasive nature of the initial intubation and significant stressors associated with procedures required during ongoing medical and nursing care.[22]

Early assessment and treatment of acute pain in ventilated infants in intensive care units is crucial. Measuring pain in a valid and reliable manner is important for monitoring the effectiveness of pain management, including determining appropriate analgesia dosing.[45,58] Although tremendous advances have been made in understanding pain responses, and more than four dozen pain measurement tools have been developed for infants, measuring pain in infants is still complex and challenging for researchers and care providers.[8,26,57] One of the issues in infant pain measurement is lack of a "gold standard" for measuring pain, as infants are unable to self-report pain.[43,55] Behavioral, physiological and multidimensional pain measurement methods are considered as surrogate approaches for self-report.[8,33,51,52] However, using behavioral indicators or vital signs in mechanically ventilated infants, especially those who are critically ill and receiving neuromuscular blockers or deep sedation, is challenging.[27]

The measurement of skin conductance (SC) is a physiological approach to measuring pain, which is based on the sympathetic nervous system response to stress.[16] When pain occurs, the stress induces sympathetic excitation and emotional sweating at an infant's

plantar (foot) or palmar (hand) regions.[30] With production and absorption of sweat in the sweat glands, the SC device monitors the increasing and decreasing electrodermal activity, records SC activity peaks and troughs, and calculates SC values.[38]

A recent scoping review, which included twenty-eight studies with 1061 infants, synthesized the validity of SC for measuring acute pain in hospitalized infants.[28] The results showed that SC might be a promising pain measurement in infants. However, inconsistent findings across the studies existed. Moreover, most included studies focused on healthy newborns or medically stable hospitalized infants, who were not receiving mechanical ventilation. Only one study reported SC for pain measurement in mechanically ventilated infants.[29] The results of this study, which included 32 infants, showed that SC was significantly higher during airway suctioning or blood sampling than at rest.[29] However, the study did not compare SC with any referent pain measures and did not compare SC values during painful procedures with those during non-painful procedures. Therefore, further research is needed before SC for pain measurement can be recommended as applicable in clinical settings, especially in critically ill infants.

This study purpose was to evaluate the validity of SC for acute pain measurement in mechanically ventilated infants in relation to: 1) the category of procedure (i.e., painful and non-painful); 2) the phase of procedure (i.e., before, during and after), and 3) referent pain measures, which are widely used in research and clinical practice.

2. Methods

2.1 Research design

A prospective cross-sectional observational design was used to study SC and its relation to referent pain measures in mechanically ventilated infants before, during and after both a painful and a non-painful procedure.

2.2 Setting and sample

The setting was a level-three neonatal intensive care unit (NICU) within a tertiary referral pediatric hospital in Canada. In order to maximize sampling, a level-three pediatric intensive care unit (PICU) within the same hospital was added as an additional clinical site after ten months of data collection. Convenience sampling was used to recruit infants in these two units. Eligibility criteria were infants up to 12 months of age, who were being mechanically ventilated, and who required a painful procedure and non-painful care (defined below).

Infants were excluded if they had conditions which would have potentially affected SC responses or precluded SC measurement, including being less than corrected gestational age of 25 weeks, and any injury to the skin where the SC probes would be placed. Also, infants with spinal cord malformation (e.g., myelomeningocele and sacral teratoma) were excluded, as these infants' behavioral pain responses may be different from infants without spinal cord malformations. Finally, as high doses of cholinergic activating/blocking drugs (e.g., neostigmine, glycopyrrolate, and atropine) may influence SC responses,[32,53] infants receiving these medications were excluded until a period of 8 hours after these medications were

administered.

The two categories of procedure (i.e., painful or non-painful) were defined based on a previous study.[1] Painful procedures were defined as intrusive interventions that involve skin breaking procedures, such as heel lance or venipuncture, or traumatic procedures, such as naso- or oro-gastric tube insertion.[1] The non-painful procedures were routine care requiring direct contact between the caregivers and the infants without any invasiveness, such as diaper change or positioning.[1]

The observation of painful or non-painful procedures was separated into the following three phases: 1) before procedure: the first 30 seconds in the three minutes prior to the painful procedure (i.e., breaking the skin or tube insertion) or non-painful procedure, 2) during procedure: the first 30 seconds following the painful or non-painful procedure, 3) after procedure: the last 30 seconds in the three minutes after completion of the painful or non-painful procedure. The separation of observation periods 1 and 3 from the procedure ensured the included infants were less likely to be handled for preparation before the procedure or settling after the procedure during these periods of observation. Thus, the data collected during these time windows would be more likely to represent the infant's conditions during baseline and recovery.

2.3 Demographic and medical information

Demographic data and medical information were collected from the patients' charts. Demographic data included gestational age (weeks + days), postnatal age (weeks + days), sex and current weight. The medical information included number of days in NICU or PICU,

diagnosis, type of most recent surgery (if applicable), number of days after most recent surgery (if applicable), mechanical ventilation mode and number of days on ventilation. In addition, medication information relating to pain or comfort management administered in the 6 hours period prior to observation was also collected, including analgesics, sedatives, muscle relaxants or anticonvulsants and their route of administration and dosage.

The Neonatal Therapeutic Intervention Scoring System (NTISS) was used as a proxy severity of illness score.[17,23,59] The NTISS is a therapy scoring system consisting of a total of 63 items.[17] Scores from one to four are assigned to items based on their therapeutic intensity and complexity, with individual items further grouped into eight categories.[4] In this study, the NTISS was scored by the first author (J. Hu) based on therapeutic interventions 24 hours prior to the data collection, which were recorded in the patients' charts. In the final calculation of scores for NTISS, points were assigned only for the most intense therapeutic intervention.[4] For example, a patient who began a scoring period with a single chest tube in place and subsequently had multiple chest tubes in place would receive final points for multiple chest tubes in place.

2.4 SC measures

The apparatus and software program used to measure SC responses in this study were commercially developed by Med-Storm Innovations.[38] The application of the apparatus and software program in this study followed the product manual.[38] The three-electrode system of the apparatus comprises a measuring electrode (black) placed on the sole of the foot, a counter current electrode (yellow) placed on either side of the ankle, and a reference voltage

electrode (blue) placed on the other side of the ankle.

2.5 Referent pain measures

There is no gold standard for pain assessment in infants.[26,39] Thus, pain in infants can only be imperfectly measured. Different referent pain measures could provide different aspects of pain experience in infants and allow researchers to understand infant pain more comprehensively.[43] Thus, two different referent pain measures were used in this study to validate SC as a measure of pain, including the Premature Infant Pain Profile-Revised (PIPP-R)[49] and the four-item subset of Neonatal Facial Coding System (NFCS)[19].

The PIPP is a 7-item multidimensional measure of pain that has been widely used to measure acute pain in infants.[50] In 2014, on the basis of a comprehensive review of the validity of PIPP for measurement of pain in infants, and feedback from researchers and clinicians, the PIPP was revised to PIPP-R to address validity and feasibility concerns in gestational age groups and behavioral states.[15,49] The PIPP-R has the same indicators but a different scoring system from the original version.[49] The PIPP-R includes three behavioral responses (facial actions: brow bulge, eye squeeze, nasolabial furrow), two physiological responses (heart rate and oxygen saturation), and two contextual items (gestational age and behavioral state). Each item is numerically scaled and scored on a 4-point scale (0 to 3 points) reflecting changes in each variable from baseline values. The scores obtained for the 7 items are summed for a total pain intensity score, ranging from 0 to 21.

The NFCS is a unidimensional single-domain measure, which consists of 10 facial expressions; however a cluster of four facial actions comprised of brow bulge, eye squeeze,

naso-labial furrow, and open lips was present in more than 90% of the infants exposed to a painful stimulus.[18,19] Each facial expression is coded as either 1 or 0 (present or absent), leading to a total score of 0 to 4. Numerous studies suggested using the most frequent facial actions, as the original ten-item NFCS is time-consuming for clinicians.[18-20,41,42] In addition, this four-item subset of the NFCS produces reliable and valid scores for pain measurement in infants, and it has also been illustrated to be feasible for use at the bedside.[20,24,25,46] Although brow bulge, eye squeeze, and naso-labial furrow have been included in PIPP-R, the indicator "open lips" in the four-item NFCS is also one of the most frequently occurring facial expression during painful procedures in infants, and the scoring standards of the indicators are different. The PIPP-R is focused on the duration of facial indicators, and the four-item NFCS pays attention to whether the facial indicators are present or not.[18,49] Thus, this four-item NFCS was also used as a referent pain measurement in this study.

2.6 Data collection procedure

The SC apparatus and video camera were set up by author J. Hu or S. M, both of whom were trained in the use of the equipment. The equipment was set up at least 10 minutes prior to the painful procedure to ensure the devices were prepared before the data collection and the infant's behavioral state had time to return to baseline after handling due to application of the SC electrodes. The infants' baseline behavioral state, highest heart rate, and lowest oxygen saturation were recorded 15 seconds prior to data collection (i.e., three minutes before a procedure), to collect the baseline data for the PIPP-R.[49] The SC and video recording commenced three minutes prior to the painful or non-painful procedure and continued for

three minutes after completion of the procedure.

The length of time between completion of data collection during a painful procedure and commencement of a non-painful procedure was at least 10 minutes, or until the infant had stabilized following the procedure. There was no attempt to standardize painful or non-painful procedures, but details of the procedures and any medication change, patient care (e.g., handling or touching) or unexpected painful procedures (e.g., an urgent airway suctioning during one of the observed procedures) during data collection were recorded.

2.7 Video coding

Video coding for the PIPP-R was done using 30 second observation time intervals.[49] Previously published time periods for observing and coding facial expressions using the four-item NFCS varied from 2 seconds to 1 minute.[5,6,18] In this study, coding the four-item NFCS via the video recording used the same observation interval as the PIPP-R, of 30 seconds.

The video recordings were divided into the 30-second segments for the three observation phases, and the sequencing of the segments was randomized. All videos were coded by two independent researchers, who were blinded to the category and phase of the procedure. The author S.M and a research assistant (J.C.) had undergone training on video coding the PIPP-R and the four-item NFCS. Training tools and education included a coding handout, education sessions, and training videos. Any discrepancies in the results of video coding were resolved through a consensus process or by consulting a third senior researcher (D.H.).

2.8 SC Value calculation

The number of SC waves per second (NWps), also referred to number of peaks per

second in the literature, was used as the parameter of SC measure in this study, as NWps has been illustrated to be the most accurate SC value for pain measurement.[35,53,54,56] NWps is the number of waves in a time window divided by the time span of the window.[38] The time window in this study was 15 seconds, which is demonstrated as an appropriate time frame by previous studies and recommended in the Med-Storm SC product manual.[7,31,38] The refreshing time was one second, which means a new value of NWps was obtained every second.[38] The maximal value of NWps, which was measured in a 30 second time period, was extracted. It was the same 30 seconds observation time interval as the two referent pain scales, before, during, and following completion of the procedure. Using the maximal value of NWps was compatible with the scoring systems of the PIPP-R and four-item NFCS, which capture the maximal intensity of facial expression, highest heart rate, and lowest oxygen saturation.[18,49]

2.9 Data analysis

Statistical analyses were performed using the IBM SPSS for Windows Version 25 statistical package (IBM Inc, Chicago, IL, USA). Continuous data such as gestational and postnatal age, pain scores of PIPP-R or the four-item NFCS, and the NWps, were described by using means, standard deviations (SD) and range if normally distributed, and medians and interquartile range (IQR) if non-normally distributed. Categorical variables such as sex, category of procedure, and medications, were summarized using frequencies and percentages. The normal distribution of the data was evaluated using the Kolmogorov-Smirnov Test.

2.9.1 Primary outcomes

There were three primary data analyses in this study to evaluate the validity of SC for acute pain measurement in mechanically ventilated infants. Parametric or nonparametric tests were used, depending on the distribution of SC data. To evaluate the validity of SC for pain measurement in relation to the category of procedure, Paired T-test or Wilcoxon signed ranks test was used to test the hypothesis: Infants being mechanically ventilated have statistically significantly different NWps during painful procedures compared to non-painful procedures. To evaluate the validity of SC in relation to the different phases of procedure, Repeated measures ANOVA (RM-ANOVA) with post hoc test or Friedman test with Dunn's multiple comparison test was used test two hypotheses: Infants being mechanically ventilated have statistically significantly different NWps during painful procedures compared to before or after painful procedures; There is no difference in NWps in infants being mechanically ventilated between during non-painful procedures and before or after non-painful procedures. To evaluate the validity of SC in relation to referent pain measures, Pearson's correlation or Spearman's correlation was analyzed to test the hypothesis: The NWps of infants being mechanically ventilated has statistically significant correlations with PIPP-R and the four-item NFCS before, during and after procedures. For inferential statistics, the probability of type I error (α) was set at 0.05, and two-tailed tests were used. The variables of missing data were deleted pairwise in data analysis.

2.9.2 Secondary outcomes

The relationships between SC and demographic and medical data were also analyzed.

Spearman's correlation was used to evaluate the association of SC with gestational age, postnatal age, current weight, number of days in NICU or PICU, number of days on ventilation, NTISS scores and time length between painful and non-painful procedures. Kruskal-Wallis test was used to evaluate the association of SC with diagnosis, mechanical ventilation mode and type of painful and non-painful procedures. Mann-Whitney U test was used to evaluate the association of SC with sex, administration of oral sucrose prior to painful procedures, and use of analgesics or sedatives administered within the 6 hours before observation.

If the findings showed the validity of SC in relation to PIPP-R in this study, diagnostic test accuracy[3] was analyzed to provide further validation of SC: how well does SC identify the presence or absence of moderate-to-severe pain in mechanically ventilated infants? The study definition of moderate-to-severe pain was if PIPP-R was greater than or equal to 13.[49,50] Receiver operator curve (ROC) analysis that described a pair of sensitivity and specificity values for every individual cut-off of SC was conducted.[34] The area under the ROC was a global measure of diagnostic accuracy and was used to estimate the degree of discriminative power of SC for pain measurement in mechanically ventilated infants.[34]

The highest Youden's index (sensitivity+specificity-1) was used to determine the optimal cut-off value of SC.[21] The measures of diagnostic test accuracy relating to this optimal cut-off value of SC were described, including sensitivity and specificity, positive and negative predictive values, and likelihood ratio for positive test results and negative test results.[36] The area under the ROC, sensitivity, specificity, and positive and negative predictive values were evaluated as excellent (value ≥90%), very good (≥80%), good (≥70%),

sufficient (≥60%) and poor (<60%).[48] The likelihood ratio for positive test results more than 10 provides a convincing ruling-in discriminative accuracy, and likelihood ratio for negative test results less than 0.1 provides a convincing ruling-out discriminative accuracy.[48]

2.10 Sample size determination

The sample size was determined to ensure that the three primary data analyses had sufficient statistical power. Fixing the probability of type I error at 5%, the sample size, 50 infants, was necessary to provide 80% power to detect a different NWps during different categories of procedure (i.e., painful and non-painful), a different NWps in the different phases of painful or non-painful procedure (i.e., before, during and after), and a relationship between NWps and the referent pain measures (i.e., the PIPP-R and the four-item NFCS). In this study, the sample size was increased to 55 infants to allow for a 10% loss of data due to technical errors in recording or other attrition reasons.

2.11 Ethical considerations

This study was approved by the affiliated hospital Research Ethics Board (17/85X) and affiliated university Research Ethics Board (A08-17-06). Potentially eligible infants were identified by unit staff in the circle of care. Parents/guardians who were interested in the study were then referred to the researchers. An explanation of the study, along with an information letter and consent form and a research media records release form, was offered by the researchers. Informed consent was voluntary and free from coercion. Parents/guardians were free to withdraw their infant from the study at any time upon their request. If an infant was withdrawn from the study, parents/guardians could choose to allow

the research team to have their infant's data already collected in the study kept for analysis or have the researchers destroy all the data.

3. Results

3.1 Sample characteristics

From October 2017 to November 2018, 130 eligible infants were identified, parents of 92 eligible infants were approached, as most parents were not available before extubating (Figure 1). Finally, 78 consents were obtained, and data for 55 infants were collected, as 23 infants had no painful procedure ordered before extubating or transfer (Figure 1). Three infants were recruited from the PICU, the other 52 infants were from the NICU, and no infant was withdrawn from the study (Figure 1). There were 25 females (45%) and 30 males (55%). The infants had a median gestational age of 35 weeks 5 days (IQR=28 weeks to 38 weeks 1 day), and the median postnatal age at study was 9 days (IQR=3 days to 39 days). The median weight was 2755 grams (IQR=1880 to 3650 grams). The infants had a median of 4 days (IQR=2 to 9 days) in NICU or PICU. The most common diagnosis was a surgical condition (n=18, 33%) and 17 of these infants underwent surgery before observation during the study period (Table 1). The mean number of days after the most recent surgery at the time of study was 5 (SD=4.62, range=1 to 18). The mean NTISS score was 15.73 (SD=3.27, range=10 to 26). To illustrate, this mean NTISS score represented a typical infant in the study who was mechanically ventilated and administered 1 to 3 antibiotic agents; had monitoring of vital signs, cardiorespiratory, noninvasive oxygen saturation and intake and output; received gavage feeding, intravenous fat emulsion, amino acid solution, insulin, and potassium, and

had phototherapy, urinary catheterization and peripheral intravenous lines in the previous 24 hours. The infants had a median of 3 days (IQR=2 to 5 days) on mechanical ventilation at the time of study. Most infants (n=29, 53%) were receiving mechanical ventilation using pressure control ventilation mode (Table 1).

3.2 Medications and procedures

Most infants (n=49, 89%) received 1 to 4 analgesics or sedative medications in the 6 hours prior to observation (Table 2). Heel lance for blood sampling (n=25, 45%) was the most commonly observed painful procedure followed by arterial puncture for blood sampling (n=11, 20%) and venipuncture for blood sampling (n=8, 15%) (Table 3). Eight infants had more than one attempt of painful procedures, and one of these infants received two types of painful procedures: heel lance for blood sampling and venous blood sampling (Table 3). In terms of non-painful procedures, every observed infant had a diaper change, but 21 of the 55 infants (38%) had diaper changed during the same study period as abdominal circumference measurement, temperature measurement, or lung auscultation (Table 3). The median time between painful and non-painful procedures was 11 minutes 20 seconds (IQR=10 minutes 28 seconds to 13 minutes 7 seconds).

3.3 Primary outcomes

Three infants had missing facial score data before, during and after painful and non-painful procedures. For these three infants, facial expressions were unable to be scored from the video footage due to the face being partially covered by tapes or tubes (Figure 1). Due to artifacts in the SC recording, two infants had missing data of NWps before, during and after

painful and non-painful procedures, two infants had missing data only before, during and after painful procedures, and three infants had missing data only before, during and after non-painful procedures (Figure 1). The median NWps was 0.27 (IQR=0.2 to 0.4) during painful procedures and 0 (IQR=0 to 0.09) during non-painful procedures. The NWps was statistically significantly higher during painful procedures compared to non-painful procedures (n=48, Z=5.71, P<0.001, effect size=0.82). The median NWps was 0 (IQR=0 to 0.07) both before and after painful procedures, 0 (IQR=0 to 0.02) before non-painful procedures, and 0 (IQR=0 to 0.07) after non-painful procedures. There was a statistically significant different NWps in the different procedure phase for painful (n=51, Chi-Square=69.90, P<0.001, effect size=0.69) and non-painful procedure (n=50, Chi-Square=19.93, P<0.001, effect size=0.20). Dunn's multiple comparison test, using Bonferroni correction, showed infants had statistically significantly different NWps according to the phase of painful procedures; with during painful procedures being higher than at baseline (n=51, Z=5.81, P<0.001, effect size=0.83) and in the recovery phase (n=51, Z=5.86, P<0.001, effect size=0.82). However, there was also statistically significantly higher NWps during non-painful procedures compared to baseline (n=50, Z 2.95, P=0.003, effect size=0.42) and recovery (n=50, Z 2.81, P=0.005, effect size=0.4). Before, during and after painful or non-painful procedures, NWps showed statistically significant positive correlations with PIPP-R (Spearman’s rho=0.4-0.62) and the four-item NFCS (Spearman’s rho=0.31-0.67) separately (Table 4).

3.4 Secondary outcomes

No statistically significant relationships between SC and demographic or medical data

were found. The area under ROC was 0.979 (95% confidence interval=0.962 to 0.996) reaching the excellent level (Figure 2). The cut-off point of 0.235 of NWps was identified having the highest Youden's index (0.88) with excellent sensitivity (92.31%), specificity (95.42%) and negative predictive value (99.21%) but only sufficient positive predictive value (66.67%) to recognize infants who scored moderate-to-severe pain on the PIPP-R. It also resulted in 20.15 likelihood ratio for positive test results and 0.08 likelihood ratio for negative test results, providing convincing ruling-in discriminative accuracy and ruling-out discriminative accuracy.

4. Discussion

4.1. Main findings

Due to the absence of a gold standard for pain measurement in infants, multiple surrogate approaches were used to validate SC measures in our study. Specifically, four hypotheses were tested to investigate the validity of SC for measuring acute pain in mechanically ventilated infants, including the relationships of SC with the category of procedure (i.e., painful and non-painful), the phase of painful and non-painful procedures (i.e., before, during and after) and referent pain measures (i.e., PIPP-R and four-item NFCS). Results showed that these hypotheses were accepted, and SC showed good validity for pain measurement in mechanically ventilated infants.

The most common validation approach in previous studies was analyzing the SC changes before, during and after painful procedures, with the aim of demonstrating whether SC responded immediately to the noxious stimuli and recovered when the noxious stimuli

ceased. Results showed a statistically significant increase in SC during the painful procedures and a statistically significant decrease after painful procedures. This finding was in agreement with 15 of the previous 16 studies using SC for pain measurement in infants[28,40] and showed good validity in relation to the three different phases of painful procedure with respect to pain measurement in mechanically ventilated infants.

In terms of non-painful procedures, there were also significant differences between different phases. The phenomena of SC responding to both painful and non-painful procedures accord with the biological mechanism of SC, which is based on how the sympathetic nervous system responds to general stress rather than pain specifically. However, the effect sizes of the SC changes before, during and after non-painful procedures were small. Additionally, the median values of NWps before, during and after non-painful procedures were all zero, although the data distributions and IQRs were different. The median and IQRs of NWps during non-painful procedures were also smaller than the SC cut-off point of moderate-to-severe pain identified in this study. These results provided evidence that the SC responses to non-painful procedures were minimal and not clinically significant. This evidence could help to illustrate that the SC values during non-painful procedures indicated the presence of a general stress response rather than pain.

Results also showed a statistically significantly higher NWps with a large effect size in infants undergoing painful procedures compared to non-painful procedures. This finding was in agreement with one previous study comparing SC during different categories of procedures (painful vs. non-painful) in healthy full-term infants.[12] This finding demonstrated that SC could distinguish painful from non-painful events in mechanically ventilated infants.

Correlations of SC with PIPP-R and the four-item NFCS indicated that the SC values had good validity for pain measurement in mechanically ventilated infants in relation to referent pain measures. However, the magnitudes of the correlations were not so high to suggest that SC and the referent pain measures are evaluating the same construct. Additionally, most of these correlations were weaker than the correlations between PIPP-R and the four-item NFCS. These findings could be expected as SC and these two referent measures are not evaluating the same dimension of pain responses in mechanically ventilated infants. SC is based on the sympathetic nervous system's response to stimuli; facial expressions in PIPP-R and the four-item NFCS are behavioral reactions, specifically, the reflexive reactions to nerve impulse transmitted to the brainstem; and the two physiological indicators in PIPP-R, changes in heart rate or oxygen saturation are induced by both the sympathetic and parasympathetic nervous system.[9,13]

There was only one previous SC study which conducted ROC analysis;[11] SC was tested in 34 infants aging from 6 to 12 months for measuring acute postoperative pain for 1 hour following arrival to the post-anesthesia care unit.[11] Although the Med-Storm SC device was also used in that study, the time window for obtaining NWps and observation time interval were set differently, at 5 seconds and 15 minutes respectively. In addition, the SC sampling method was not reported. The results showed the cut-off point of NWps for discriminating moderate-to-severe pain (i.e., NFCS$\geqslant$4 out of 9 points) was 0.571.[11] It also reported that this cut-off point had a sensitivity of 54.5%, a specificity of 79.4%, a positive predictive value of 21.4%, and a negative predictive value of 94.4%.[11] Compared to this previous study[11], the cut-off point in our study was much lower, and the outcomes of ROC analysis had better

performance. The difference was not only caused by the different referent pain measurements used in the ROC analysis, but also probably due to the different populations, pain-related contexts, and SC calculation methods.

The low likelihood ratio for negative test result and the excellent specificity and negative predictive value indicated that SC was able to detect an infant without moderate-to-severe pain based on the negative SC result (i.e., NWps<0.235). The high likelihood ratio for positive test result and excellent sensitivity indicated that SC was able to detect an infant with moderate-to-severe pain based on the positive SC result. However, the positive predictive value did not reach an excellent level and indicated that one-third of infants, who had positive results, were incorrectly considered as having moderate-to-severe pain and could be overtreated, if they received pain treatments based on SC results.

4.2 Implications for clinical practice and future research

Six decades ago, Beecher reviewed challenges in the use of subjective responses to pain in research and clinical practice.[2] Since then, there has been a drive for objective indicators of pain.[44] Utilizing SC to measure pain in infants is more objective than using facial expressions or body movements especially in sick and preterm infants whose behavioral responses may be less obvious or unable to be assessed. The SC measurement device is quick and straightforward to use, requires a short training time and the scores of SC can be easily and quickly understood by clinicians and researchers. The findings in this study showed that SC is a promising approach to measuring pain in mechanically ventilated infants. Thus, SC has potential as a routine clinically useful measure of pain and as an outcome evaluating the

effectiveness of pain treatments in critically infants, who require painful procedures as part of their nursing and medical care.

However, the values of SC must be interpreted with caution, due to the imperfect correlations with the referent pain measures and low positive predictive value. It is useful to use SC with other pain scales, for example, PIPP-R and the four-item NFCS, as these scales provided a different dimension of pain in infants from SC and may exclude the false positive cases compared to when only using SC. Additionally, pain measurement using SC needs to be considered along with the status of the individual infant, personal expression, and pain-related context.[10,14,47]

This study did not test the validity of SC for pain measurement in relation to pain treatment. This response is important as a valid pain measurement should be able to detect a change in pain due to the implemented pain treatments. In further clinical trials, NWps could be used as an outcome in addition to behavioral pain scales to evaluate the effectiveness of pain treatments in critically ill infants. In addition, the existence of SC artifacts might be a practical issue of using SC in clinical settings and decrease its reliability. Thus, translational research using an interdisciplinary collaborative approach between technologists and pain scientists is warranted to advance the technology of measuring SC and reduce artifacts or other mechanical failures.

4.3 Strengths and limitations

This study compared SC during painful and non-painful procedures, in the three different phases of procedure and also compared SC with other pain measures which are

commonly used in the clinical and research setting. These comparisons provided comprehensive validity of SC for pain measurement in mechanically ventilated infants. Additionally, this study provided detailed information on SC value calculation, including the time window for obtaining NWps (i.e., 15 seconds), refreshing time (i.e., 1 second), observation time interval (i.e., 30 seconds) and SC sampling method (i.e., maximal value). This detailed design and reporting reduced bias and enables replication of the study. Last, this study used ROC analysis to determine the diagnostic test accuracy of SC based on the validity of SC in relation to PIPP-R. This analysis provided further information on the discriminative performance of SC to recognize moderate-to-severe pain in mechanically ventilated infants.

Despite the study strengths, there were also limitations to the study. First, this study was an observational study, and there was no attempt to standardize painful or non-painful procedures and pain treatments. Potential influencing variables in mechanically ventilated infants during data collection were not controlled. However, the dependent group statistics were used in this study to ensure that the pair of data was from the same patient during similar context. Second, the validation approaches in this study were based on the assumptions that skin-breaking procedures and traumatic procedures are painful, and diaper change, along with other nursing care, is stressful but not painful, and the scores of PIPP-R and four-item NFCS showed good validity in infant pain measures. However, these assumptions could be challenged.

5. Conclusion

In this study, SC showed good validity in relation to category of procedure, phase of procedure and referent pain measures. SC is a potential approach to measuring pain in critically ill infants requiring mechanical ventilation. However, further research testing the validity of SC in relation to pain treatments and advancing the technology of measuring SC is needed before it can be recommended for routine clinical use.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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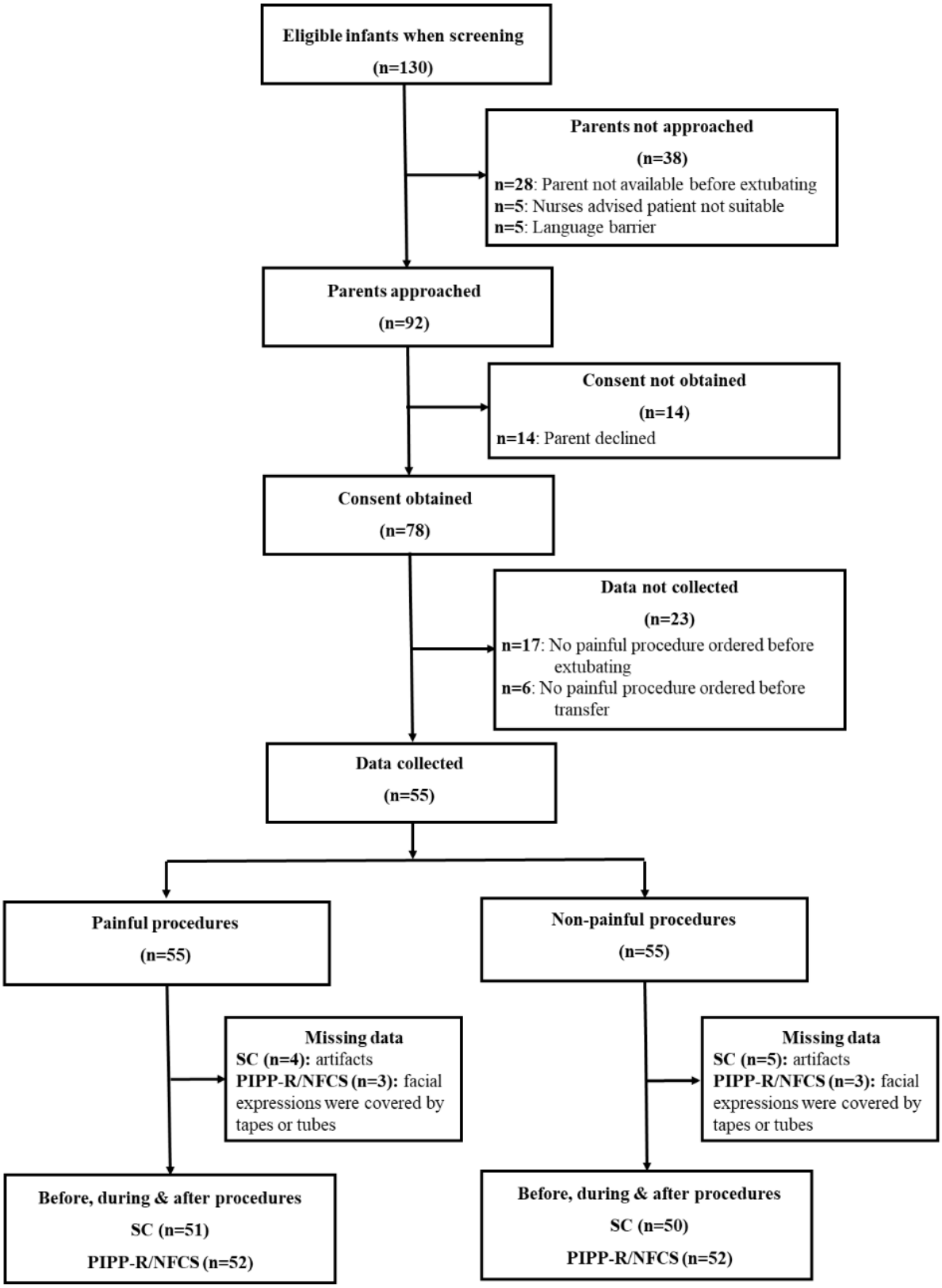

Figure 3- 1. Patient recruitment flow diagram

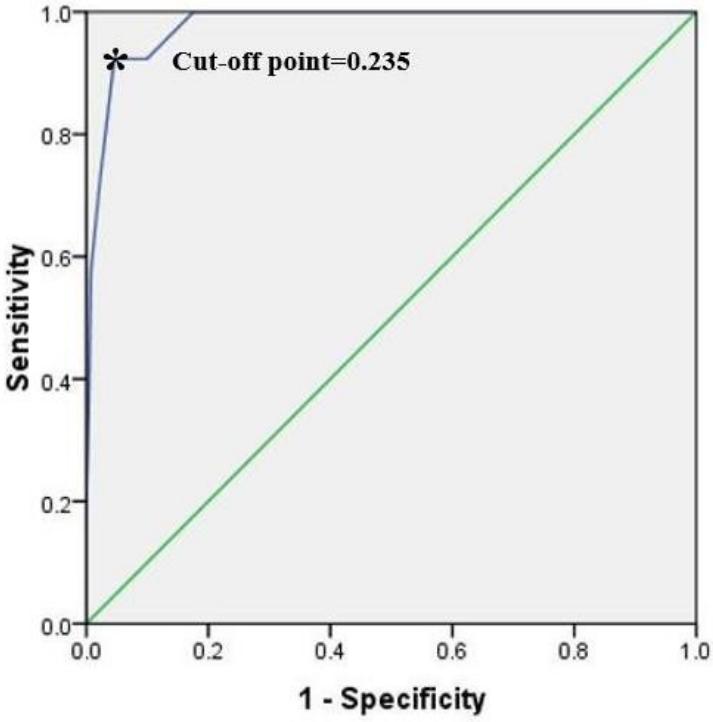

Figure 3- 2. The ROC of NWps to discriminate the moderate to severe pain

Table 3- 1. Sample characteristics (N=55)

Variable	**Frequency (%)**
Diagnostics	
Surgical condition	18 (33)
Respiratory disease	15 (27)
Cardiac disease	11 (20)
Sepsis	6 (11)
General medical disease	3 (5)
Non-surgical congenital anomalies	2 (4)
Type of surgery	
Major abdominal surgery	8 (46)
Cardiac surgery	3 (18)
Major chest surgery	2 (12)
Percutaneous drain insertion	2 (12)
Neurosurgical surgery	1 (6)
Endoscopy	1 (6)
Ventilation mode	
Pressure Control Ventilation	29 (53)
Volume Control Ventilation	20 (36)
High Frequency Oscillation	6 (11)

Table 3- 2. Analgesic/Sedation medications (n=55)

Medication[a]	**Delivery method**	**Number of doses**	**Median (IQR) of dosing**
Acetaminophen	Oral	1	10 mg/kg
Ibuprofen	Oral	1	10 mg/kg
Fentanyl	Intravenous bolus	17	2 mcg/kg (1.1-2)
	Intravenous infusion	24	2 mcg/kg/h (0.9-3)
Morphine	Intravenous bolus	10	60 mcg/kg (50-100)
	Intravenous infusion	11	30 mcg/kg/h (20-60)
Sucrose	Oral	22	0.2 ml
Ketamine	Intravenous bolus	3	500 mcg/kg (100-1000)
	Intravenous infusion	1	500 mcg/kg/h
Midazolam	Intravenous bolus	2	50 mcg/kg (50-50)
	Intravenous infusion	2	12.5 mcg/kg/h (10-15)

Note.

a. Medications administered within the 6 hours before observation

Table 3- 3. Painful and non-painful procedures (n=55)

Variable	**Frequency (%)**
Type of painful procedures	
Heel lance for blood sampling	25 (45)
Arterial puncture for blood sampling	11 (20)
Venipuncture for blood sampling	8 (15)
Intravenous insertion	6 (11)
Nasogastric tube insertion	4 (7)
Heel lance for blood sampling & Venipuncture for blood sampling	1 (2)
Number of attempts of painful procedures	
1	47 (85)
2	6 (11)
3	1 (2)
4	1 (2)
Type of non-painful procedures	
Diaper change	34 (62)
Diaper change, abdominal circumference measurement, temperature measurement, lung auscultation	13 (24)
Diaper change, temperature measurement, lung auscultation	8 (14)

Table 3- 4. The validity of SC in relation to referent pain measurements

Different phase and procedure	**Correlations**		
Before painful procedures		PIPP-R (0, 0-6)[a]	NFCS (0, 0-0)
	SC	r[b]=0.50 (n=48, p=0.000)	r=0.35 (n=48, p=0.015)
	r(PIPP-R* NFCS)=0.41 (n=52, p=0.002)		
During painful procedures		PIPP-R (13, 7.25-16)	NFCS (3, 0.25-4)
	SC	r=0.62 (n=48, p<0.001)	r=0.67 (n=48, p<0.001)
	r(PIPP-R* NFCS)=0.87 (n=52, p<0.001)		
After painful procedures		PIPP-R (5.5, 0-7)	NFCS (0, 0-0.75)
	SC	r=0.46 (n=48, p=0.001)	r=0.31 (n=48, p=0.034)
	r(PIPP-R* NFCS)=0.56 (n=52, p<0.001)		
Before non-painful procedures		PIPP-R (0, 0-0)	NFCS (0, 0-0)
	SC	r=0.40 (n=48, p<0.001)	r=0.33 (n=48, p<0.001)
	r(PIPP-R* NFCS)=0.86 (n=53, p<0.001)		
During non-painful procedures		PIPP-R (0, 0-6)	NFCS (0, 0-1)
	SC	r=0.54 (n=48, p<0.001)	r=0.49 (n=48, p<0.001)
	r(PIPP-R* NFCS)=0.67 (n=53, p<0.001)		
After non-painful procedures		PIPP-R (0, 0-3.75)	NFCS (0, 0-0)
	SC	r=0.42 (n=48, p<0.001)	r=0.35 (n=48, p<0.001)
	r(PIPP-R* NFCS)=0.69 (n=53, p<0.001)		

Note: [a] median, interquartile range

[b] r=Spearman's rho

Chapter 4: Integrated Discussion

Overview

Measuring pain in infants is important but remains complex and challenging for researchers and HCPs despite much work over the years improving the understanding of pain assessment. This dissertation provides insight on the validity of SC for pain assessment in infants and consists of two studies: 1) a scoping review synthesizing the methods and findings of previous published studies on validating or using SC for measuring acute pain in infants (Hu, Modanloo, Squires, Harrold, & Harrison, 2019); 2) a primary study evaluating the validity of SC for measuring acute pain in mechanically ventilated infants (Hu, Harrold, Squires, Modanloo, & Harrison, 2019).

The relational validity evidence in the AERA Standards for Psychological Testing was used to guide the evaluation of the validity of SC in this dissertation (American Educational Research Association, 2014). The scoping review (Study One) focused on the validity evidence of SC for pain measurement in relation to referent pain measures, stimuli, age, and other contextual variables (Hu, Modanloo, et al., 2019). The primary study (Study Two) focused on the validity of SC for pain measurement in relation to category of procedure (i.e., painful and non-painful), phase of painful or non-painful procedure (i.e., before, during and after), and referent pain measures (i.e., the PIPP-R and the four-item NFCS subset) (Hu, Harrold, et al., 2019).

The scoping review involved searching for and analyzing published literature on validity evidence of SC for pain assessment in infants (Hu, Modanloo, et al., 2019). Knowledge gaps

and research areas that need improvement in the studies of validating SC in infants were subsequently identified. Additionally, the findings informed the target population in the primary study, who were infants requiring invasive mechanical ventilation (Hu, Harrold, et al., 2019). These critically ill infants are one of the most vulnerable populations, who may benefit from SC being used for pain measurement but have rarely been included in previous SC studies. Finally, the findings in this review also informed the different sources of relational validity of SC, research design, methods and reporting for the primary study (Hu, Harrold, et al., 2019). The primary study evaluated the validity of SC for acute pain measurement in mechanically ventilated infants in relation to category of procedure (painful compared to non-painful), phase of procedure (before, during and after) and referent pain measures (PIPP-R and the four-item NFCS) (Hu, Harrold, et al., 2019). The diagnostic test accuracy of SC for measuring moderate to severe pain based on the PIPP-R score was also determined. Findings of the primary study (Hu, Harrold, et al., 2019) were compared with studies included in the scoping review (Hu, Modanloo, et al., 2019), and the recent studies published following completion of the scoping review. Findings from the primary study (Hu, Harrold, et al., 2019) contribute valuable information to the knowledge of pain assessment in infants, and highlights that SC has the potential to provide a promising method of pain measurement in mechanically ventilated infants, which in turn, may lead to an improvement in pain management in this vulnerable population. Results also contribute to the methodology of validating SC in infants and has implications for clinical practice, education, leadership, policy, and research.

Given that the findings of each of the two studies in this dissertation have been

discussed separately in each manuscript, the purpose of this chapter is to briefly summarize the key findings of the two studies. Moreover, the integrated discussion of these findings is provided in further detail and situated within the current body of knowledge as it relates to SC for pain measurement. Finally, the discussion is followed by contributions of the findings to the broader literature, implications for clinical practice, recommendations for future research, limitations of each study, knowledge dissemination, and conclusions.

Summary of findings

Twenty-eight studies with 1061 infants were included in the scoping review (Hu, Modanloo, et al., 2019), of which 23 were cross-sectional observational studies and five were interventional studies. The populations in the studies included healthy infants (n=12 studies), infants with mild severity of illness who were breathing spontaneously with no analgesics, sedation or neuromuscular blockers (n=13) and infants receiving analgesics, sedatives or neuromuscular blockers (n=3). The validity evidence of SC was tested in relation to referent pain measures (13 variables), stimuli (13 variables), age (2 variables) and other contextual variables (11 variables). The validity evidence of SC in relation to vital signs was tested, which specifically included heart rate in eight studies, oxygen saturation in six studies, and respiratory rate in two studies. SC was poorly correlated with respiratory rate and oxygen saturation in all studies, but SC had moderate positive correlation with heart rate in two of the eight studies (25%). SC was moderately positively correlated with the unidimensional behavioral pain assessment scales (i.e., NFCS, COMFORT-b, ABC Pain Scale) or indicator (i.e., crying time); however, SC was poorly correlated with multidimensional scales

(including behaviors and vital signs or state of awareness, for example, Neonatal Infant Pain Scale, PIPP, N-PASS, and Bernese Pain Scale for Neonates). The validity evidence of SC in relation to phase of painful procedure (i.e., before, during and after) was tested in 15 studies, and SC increased significantly during painful procedures in most studies (n=14/15, 93%). However, SC also increased significantly during non-painful procedures in five of seven studies (71%), which evaluated the validity evidence of SC in relation to phase of non-painful procedure. Recommendations for routine clinical use of SC in infant pain measurement could not be generated due to inconsistent findings on validity evidence and wide variation in methods across studies, and ongoing key knowledge gaps in the field.

The primary study (Hu, Harrold, et al., 2019) in this thesis included 55 eligible infants (30 male and 25 female) in intensive care units, aged from newborn up to 12 months of age, who were mechanically ventilated, and required a painful and non-painful procedure. SC (NWps) during painful procedures (median 0.27, interquartile range (IQR) 0.2-0.4) was statistically significantly higher than those during non-painful procedures (0, 0-0.09). SC (0.27, 0.20-0.40) during painful procedures were statistically significantly higher than those before (0, 0-0.07) and after painful procedures (0, 0-0.07). SC showed moderate statistically signficant positive correlations with PIPP-R (Spearman's rho=0.4-0.62) and the four-item NFCS (Spearman's rho=0.31-0.67) before, during and after painful or non-painful procedures respectively. SC had excellent performance (area under the receiver operator curve (ROC)=0.979) with excellent sensitivity (92.3%), specificity (95.4%) and negative predictive value (99.2%) but only sufficient positive predictive value (66.7%) when used to discriminate moderate or severe pain. SC has potential as a routine clinically useful measure of pain and as

an outcome evaluating the effectiveness of pain treatments in critically infants, who require painful procedures as part of their nursing and medical care.

Discussion

The use of SC is a novel and emerging method of measurement of acute pain and stress in infants. Twenty-eight published studies of relating to SC for pain measurement in infants were included in the scoping review (Hu, Modanloo, et al., 2019). An updated search to April 21, 2019 identified four additional eligible studies (Maillard, Garnier, Saliba, & Favrais, 2019; Oji-Mmuo et al., 2019; Passariello et al., 2019; Roue et al., 2018), which were published after the completion of the scoping review (Hu, Modanloo, et al., 2019). Thus, there have been 32 published articles in this field. The four additional eligible articles have also been integrated into this discussion. There is an increase in the number of recently published studies using SC to assess acute pain in infants, with most of the studies being published in the last 10 years.

Due to the absence of a gold standard for pain measurement in infants, it is necessary to test multiple sources of validity of SC for pain measurement in infants, including relation to category of procedure, phase of procedure, and referent pain measures. However, most previous studies only tested one or two sources of validity in infants. In this thesis, the primary study compared SC during painful and non-painful procedures, in three different phases of procedure (before, during, after) and compared SC with two referent pain measures (PIPP-R, the four-item NFCS) which are commonly used in the clinical and research setting (Hu, Harrold, et al., 2019). These multiple comparisons in the same population of infants at

the same time provided comprehensive validity evidence of SC for measuring pain in mechanically ventilated infants.

Findings from the scoping review (Hu, Modanloo, et al., 2019) showed that the SC measurement device from Med-Storm Innovations was the most commonly used device in infants (Med-Storm Innovation AS, 2012). The Med-Storm SC device allows for measurement of seven SC parameters, including mean SC level, NWps, area under curve, area huge peaks, area small peaks, average rise time and average peak. The NWps, also sometimes referred to as number of peaks per second in the literature, was used in all previous studies, except the first study in 1990 (Gladman & Chiswick, 1990). It has been illustrated to be the most accurate SC parameter for pain measurement not only in infants, but also in children and adults (Macko et al., 2014; Storm, 2008, 2013; Valkenburg et al., 2012). Thus, NWps was used as the parameter of SC in the primary study (Hu, Harrold, et al., 2019).

Validity evidence in relation to phase of painful procedure

The primary study results showed that there was a statistically significant difference with large effect size in the SC value of NWps in mechanically ventilated infants before, during and after painful procedures (Hu, Harrold, et al., 2019). SC values during painful procedures were significantly higher than those both in the baseline and recovery with large effect sizes. These findings illustrated that SC showed good validity evidence in relation to the different phases of painful procedures with respect to pain measurement in mechanically ventilated infants.

Comparing SC before, during and after painful procedures was the most common

validation approach in previous studies evaluating the validity of SC for pain measurement in infants. Fifteen of the 28 studies included in the scoping review (Hu, Modanloo, et al., 2019), as well as one recent study (Passariello et al., 2019) published after the completion of the scoping review, tested the validity of SC in relation to phase of painful procedure. The findings in the primary study (Hu, Harrold, et al., 2019) were in agreement with 14 of the 15 studies in the scoping review (Hu, Modanloo, et al., 2019), and one recently published study (Passariello et al., 2019). These 14 studies in the scoping review (Hu, Modanloo, et al., 2019) included six studies of preterm infants (i.e., 22 to 36 weeks gestation), five studies of full-term infants and three studies of both preterm and full-term infants. The results in all these studies showed there was a statistically significantly higher NWps during painful procedures compared to baseline and recovery. In the most recent study that was not included in the scoping review (Hu, Modanloo, et al., 2019), fifty-six full-term newborns were recruited (Passariello et al., 2019). The NWps were also statistically significantly higher during capillary or arterial puncture for blood sampling compared to baseline and recovery period (Passariello et al., 2019). Only Schubach et al., (2016) did not find validity evidence of SC in relation to phase of painful procedure. This study was conducted in two groups of full-term newborns, including 12 full-term newborns with opiate-induced neonatal abstinence syndrome and 12 unexposed full-term newborns (Schubach et al., 2016). Neither group showed a statistically significant change of SC in response to the heel lance (Schubach et al., 2016). However, these non statistically significant findings in the study may be attributed to the small sample sizes in each group (Schubach et al., 2016).

The sample size estimation was rarely reported or conducted in previously published

studies of validating or using SC for pain measurement in infants. The methods of determining sample sizes were reported in only two of the 32 published studies (Passariello et al., 2019; Tristao, Garcia, de Jesus, & Tomaz, 2013). In the primary study, the sample size was determined to ensure that four hypothesis tests had sufficient statistical power (Hu, Harrold, et al., 2019).

In the 32 previously published SC studies, there were two different kinds of painful procedures: skin-breaking procedures, including heel lance, intravenous insertion, arterial puncture or venipuncture or capillary for blood sampling, and intramuscular injection and traumatic procedures, including airway tube insertion and airway suctioning. The primary study included all types of skin-breaking procedures and only two types of traumatic procedures: naso- and oro-gastric tube insertion (Hu, Harrold, et al., 2019). Although airway suctioning is one of the most commonly performed procedures in mechanically ventilated infants, consensus has not been reached whether it is considered as a stressful or painful procedure (Lucchini, Canesi, Robustelli, Fumagalli, & Bambi, 2016). Additionally, airway suctioning potentially influences heart rate and oxygen saturation regardless of whether actual pain is caused, yet these changes would be reflected in total PIPP-R scores. Thus, the primary study did not include airway suctioning (Hu, Harrold, et al., 2019).

Validity evidence in relation to phase of non-painful procedure

The results in the primary study showed that there was a statistically significant difference in SC in mechanically ventilated infants before, during and after non-painful procedures (Hu, Harrold, et al., 2019). The results in the post hoc tests also showed that SC

values during non-painful procedures were significantly higher than those both in the baseline and recovery. The phenomenon of SC responding to both painful and non-painful procedures accords with the biological mechanism of SC, which is based on how the sympathetic nervous system responds to general stress rather than pain specifically. However, not all stress is painful. The effect sizes for these statistical tests were small. In addition, the median SC before, during and after non-painful procedures were all zero, although the data distributions and IQRs were different. The median and IQRs of NWps during non-painful procedures were smaller than the SC cut-off point of moderate to severe pain identified in the primary study (Hu, Harrold, et al., 2019). These results provided evidence that the SC responses to non-painful procedures were minimal and not clinically significant, although the change was statistically significant. This evidence could also help to illustrate that the SC values during non-painful procedures indicated the presence of a general stress response rather than pain in mechanically ventilated infants.

Seven studies included in the scoping review evaluated SC responses during non-painful procedures (Hu, Modanloo, et al., 2019). In four of these seven studies, a statistically significantly different NWps was reported in different phases of the non-painful procedures (before, during, after) (Hernes et al., 2002; Lyngstad et al., 2014; Salavitabar et al., 2010; Zeiner, Storm, & Doheny, 2016). Two studies used auditory stimuli as a non-painful procedure (Hernes et al., 2002; Salavitabar et al., 2010). The findings in both studies showed that infants had statistically significantly higher NWps during auditory stimuli than during exposure to baseline sound levels. Salavitabar et al., (2010) reported that the sound level of their auditory stimuli was greater than 65 decibels and the baseline sound level was lower

than 55 decibels, but Hernes et al., (2002) did not provide these relevant sound levels. Lyngstad et al., (2014) included 17 preterm infants in their study and showed that NWps was statistically significantly higher during diaper change than baseline and recovery. In Zeiner et al., (2016) study, 30 preterm infants not only received diaper change, but also axillary temperature, assessment and repositioning as clustered nursing care. Zeiner et al., (2016) reported that NWps statistically significantly increased from before to during the clustered nursing care. The results of these four studies illustrated that SC increases statistically significantly during non-painful procedures compared to baseline and recovery.

The results of the scoping review (Hu, Modanloo, et al., 2019) also showed that two of the seven studies which evaluated SC during non-painful procedures did not find statistically significantly different NWps in different phases of non-painful procedures (Harrison et al., 2006; Munsters, Wallstrom, Agren, Norsted, & Sindelar, 2012). Twelve infants in the study by Harrison et al., (2006) and ten preterm newborns in the study by Munsters et al., (2012) had NWps recorded during a diaper change and clustered tactile stimuli (i.e., feeding using syringe and auscultation using stethoscope) respectively. However, the non-painful procedures did not result in any statistically significant SC changes in either study.

The remaining study which examined SC during non-painful procedures included in the scoping review (Hu, Modanloo, et al., 2019) studied four different age groups of infants: preterm newborns (i.e., up to one week old postnatal age), preterm infants in the post-neonatal period (i.e., more than one week old postnatal age), full-term newborns and three months old full-term infants (Hellerud & Storm, 2002). Eight participating infants in each age group received nursery handling (Hellerud & Storm, 2002). Full-term infants aged 3 months

old had different SC responses to non-painful procedures compared to the other three age groups. These older infants did not have statistically significantly increased SC during nursery handling; however, the preterm and full-term newborns and preterm infant in the post-neonatal period had statistically significantly increased SC values, including mean SC level, NWps and area under curve (Hellerud & Storm, 2002). Thus, the findings of these seven studies, which were identified in the scoping review (Hu, Modanloo, et al., 2019), on the validity evidence of SC in relation to phase of non-painful procedure were inconsistent.

As the biological mechanism of SC is based on how the sympathetic nervous system responds to general stress, it is expected that SC will increase during procedures that are stressful as well as procedures that are painful to infants. It is difficult to make a judgment about whether the SC values during non-painful procedures indicate the presence of general stress or pain specifically when these studies did not compare these SC values with those during painful procedures in the same group of infants in the same contexts. In addition, it is difficult to explain the statistical significance when only the significant p values were reported in the studies (Staggs, 2019; Wasserstein, Schirm, & Lazar, 2019). Using absolute and standardized effect sizes has been recommended to fully understand the results and the magnitude of different values between groups (Sullivan & Feinn, 2012). Last, it is difficult to determine the clinical significance of the SC results in these seven studies (Harrison et al., 2006; Hellerud & Storm, 2002; Hernes et al., 2002; Lyngstad et al., 2014; Munsters et al., 2012; Salavitabar et al., 2010; Zeiner et al., 2016), as these studies did not compare SC with any referent pain measures and did not identify the cut-off points of SC for different levels of pain intensity in infants. Thus, although they reported the different values in different phases

of non-painful procedures, the clinical meaning and the level of pain intensity related to these values and changes were not clear.

Most of the studies validating SC in infants, including the primary study (Hu, Harrold, et al., 2019), were observational studies, and the non-painful procedures were not standardized. The non-painful procedures in the previous studies included external environment stress, such as auditory stimuli, one single non-painful procedure, such as diaper change, and multiple non-painful procedures at the same period, such as nursing care or handling, including axillary temperature, assessment and diaper change, and clustered tactile stimuli, including feeding using syringe and auscultation using stethoscope. In the primary study, most mechanically ventilated infants had only a diaper change, but around 40% of infants had diaper change during the same study period as abdominal circumference measurement, temperature measurement, and lung auscultation (Hu, Harrold, et al., 2019). This clustering of care, which means to perform multiple procedures together, has been widely studied and commonly used in clinical settings (Burke, 2018; Ohlsson & Jacobs, 2013). These practices were initially emphasized by the Newborn Individualized Developmental Care and Assessment Program introduced by Als in the mid 1980s (Als, 1986). The main goal of clustering care is allowing the infant to have longer periods of uninterrupted sleep and rest (Hack, 2009; Valizadeh, Avazeh, Bagher Hosseini, & Asghari Jafarabad, 2014).

Validity evidence in relation to category of procedure

In the primary study, there was a statistically significantly higher NWps with a large effect size in mechanically ventilated infants undergoing painful procedures compared to

non-painful procedures (Hu, Harrold, et al., 2019). This finding demonstrated that SC could distinguish painful events from non-painful events in mechanically ventilated infants. This finding was in agreement with one previous study comparing SC during different categories of procedures (painful vs. non-painful) in 27 healthy full-term infants (Eriksson, Storm, Fremming, & Schollin, 2008).

However, the details of the data collection processes were different in the primary study (Hu, Harrold, et al., 2019) and the Eriksson et al., (2008) study. First, the painful and non-painful procedures in the study by Eriksson et al., (2008) were different from those in the primary study (Hu, Harrold, et al., 2019). Each infant in Eriksson et al., (2008) study underwent two procedures: painful procedures performed as heel lance for blood sampling and non-painful procedures performed as distinct touching by the caregiver's hand on each infant's arm for 30 seconds.

Second, the sequence of painful and non-painful procedure was different. The different category of procedure was performed in a randomized order on each infant in the study by Eriksson et al., (2008). The randomized sequence of procedures was feasible in their study, as they used the infant's arm touching as the non-painful procedure in their study. However, the primary study rigorously followed observational research design, and there was no change in the normal care given to the infants during procedures in clinical settings (Hu, Harrold, et al., 2019). In the primary study, infants always had painful procedures before non-painful procedures, both of which were provided together, as we aimed to provide these two categories of procedures to the same infant in the same context (Hu, Harrold, et al., 2019). In this way, we also could reduce the risk of having any loss of data when the data during non-

painful procedures had been collected but painful procedures were cancelled, or infants were transferred before painful procedures were performed/required.

Third, the preparation time before the procedure to set up the SC device and stabilize the SC values was different. In the Eriksson et al., (2008) study, the preparation time before the beginning of the first procedure was one minute (Eriksson et al., 2008). After each procedure, the infant was left undisturbed on the bed for approximately 5 minutes before the next procedure began (Eriksson et al., 2008). Besides this study, the scoping review identified 16 studies, which reported preparation time to set up the SC device and stabilize the SC values, ranging from one minute to 30 minutes (Hu, Modanloo, et al., 2019). Ten minutes (n=6) and five minutes (n=5) preparations were the two most commonly used time lengths. In the primary study, the SC apparatus and video camera were set up at least 10 minutes prior to the painful procedure to ensure the devices were prepared before the data collection and the infant's behavioural state had time to return to baseline after handling due to the application of the SC electrodes (Hu, Harrold, et al., 2019). The length of time between completion of data collection during a painful procedure and commencement of a non-painful procedure was also planned to be at least 10 minutes, or until the infant had stabilized following the painful procedure. In the 55 infants included in the primary study, the median time between painful and non-painful procedures was 11 minutes 20 seconds (IQR=10 minutes 28 seconds to 13 minutes 7 seconds). These time intervals were long enough to stabilize SC in the infants yet not long enough for the infant's clinical condition to change (Bossuyt et al., 2015; Whiting et al., 2011). Thus, the primary study had a low probability that the infants' conditions and the medical context which they were in changed significantly from

undergoing painful procedures to non-painful procedures (Hu, Harrold, et al., 2019).

Validity evidence in relation to referent pain measures

In the primary study, NWps showed moderate statistically significant positive correlations with PIPP-R and the four-item NFCS before, during and after painful or non-painful procedures (Hu, Harrold, et al., 2019). This finding indicated that the SC values had good validity for pain measurement in mechanically ventilated infants in relation to referent pain measures. However, the magnitudes of these correlations were not so high to suggest that SC and the referent pain measures are evaluating the same construct. Additionally, most of these correlations were weaker than the correlations between PIPP-R and the four-item NFCS. These findings could be expected as SC and these two referent measures are not evaluating the same dimension of pain responses in mechanically ventilated infants. SC is based on the sympathetic nervous system's response to stimuli; facial expressions in PIPP-R and the four-item NFCS are behavioural reactions; specifically, the reflexive reactions to nerve impulse transmitted to the brainstem; and the two physiological indicators in PIPP-R, changes in heart rate or oxygen saturation are induced by both the sympathetic and parasympathetic nervous system (Cowen et al., 2015; Fitzgerald, 2015).

Twenty of the 28 studies included in the scoping review (Hu, Modanloo, et al., 2019), and the three more recently published studies (Maillard et al., 2019; Oji-Mmuo et al., 2019; Roue et al., 2018) published after the scoping review, tested validity evidence of SC in relation to referent pain measures. The results of these studies showed that SC was moderately positively correlated with unidimensional behavioral pain assessment scales or

crying time; however, SC was poorly correlated with multidimensional scales. Among these studies, only one study compared NWps with PIPP in 27 healthy full-term infants undergoing heel lance for blood sampling and tactile stimuli (Eriksson et al., 2008), and their findings did not demonstrate a statistically significant correlation between SC and PIPP (Eriksson et al., 2008). Four studies compared NWps with NFCS, including two studies (Dalal et al., 2013; de Jesus, Campos Junior, Storm, Da Rocha, & Tristao, 2015) identified in the scoping review (Hu, Modanloo, et al., 2019) and two studies (Oji-Mmuo et al., 2019; Roue et al., 2018) published after the scoping review. In three of these four studies, there was a moderate statistically significant positive relationship, as analyzed by Kendall's rank correlation coefficient 0.4 ($p=0.006$) in 34 infants aging from 6 months to 12 months for measuring acute postoperative pain (Dalal et al., 2013); Pearson correlation coefficient 0.41 ($p<0.001$) in 103 healthy full-term newborns undergoing venipuncture for systematic neonatal screening (Roue et al., 2018); and Spearman correlation coefficient 0.43 ($p=0.016$) in 22 opioid-exposed and 15 healthy full-term newborns undergoing heel lance for neonatal metabolic screening (Oji-Mmuo et al., 2019). These correlation coefficients were similar to the results in the primary study (Hu, Harrold, et al., 2019), which were also in the range of medium effect sizes. However, de Jesus et al., (2015) did not find statistically significant correlations of NWps and area under curve respectively with NFCS in 41 healthy full-term newborns undergoing heel lance for blood sampling (de Jesus et al., 2015).

The scoping review (Hu, Modanloo, et al., 2019) also identified many other referent pain measures, which included three vital signs (heart rate, respiratory rate, oxygen saturation); crying time; salivary cortisol; two scales for state of arousal and general

movements (Prechtl's scale, Newborn Individualized Development Care and Assessment Program); two other unidimensional measures (COMFORT-b, ABC pain scale); and three other multidimensional measures (Neonatal Pain Agitation and Sedation Scale, Neonatal Infant Pain Scale, and Bernese Pain Scale for Neonates). The findings on the validity of SC in relation to these referent pain measures have been described in the scoping review (Hu, Modanloo, et al., 2019). One recently published study compared NWps with Acute Pain in Newborn Infants Scale, which comprises three behavioral responses, in 34 very preterm infants at term-equivalent age and 34 healthy full-term neonates, before and at three different time points (15, 45 and 90 seconds) after hip dysplasia screening (Maillard et al., 2019). Results of this study illustrated a moderate statistically significant positive correlation of SC with the pain behavioural scale in both groups, however only at the 15-second period after hip dysplasia screening (Maillard et al., 2019). The reasons that the primary study did not use these pain measurements as references have been explained in detail in the thesis introduction and the methods of our manuscript two (Hu, Harrold, et al., 2019).

In terms of Prechtl's behavioural scale, it was used in eight studies as a referent pain measure. There was a statistically significant positive relationship between SC and Prechtl's scale in five of the eight studies (Gladman & Chiswick, 1990; Hernes et al., 2002; Schubach et al., 2016; Storm, 2001b; Storm & Fremming, 2002). Additionally, the Med-Storm SC Product Manual recommended the different cut-off points of the NWps to measure pain intensity compared to different behavioural states according to Prechtl's scale (Med-Storm Innovation AS, 2012). However, the specific correlation coefficients were not reported in the studies, and the methods of determining the cut-off points of the NWps were not described in

the manual. Most importantly, Prechtl's scale was developed to measure the state of arousal and general movements, and it did not show acceptable reliability and validity with respect to pain measurement in infants (Darsaklis, Snider, Majnemer, & Mazer, 2011). Thus, the primary study did not use Prechtl's scale as a referent pain measurement (Hu, Harrold, et al., 2019).

In the primary study, the correlations of NWps with PIPP-R and the four-item NFCS were analyzed separately before, during and after painful and non-painful procedures (Hu, Harrold, et al., 2019). However, the SC values and pain scores from repeated measures were not combined and analyzed at the same time to obtain a general correlation coefficient between NWps and PIPP-R or NWps and the four-item NFCS in mechanically ventilated infants. This analysis approach increases the risk of producing erroneous results, as it violates one assumption of the Pearson or Spearman correlation analysis, which is assuming independence of error between observations (Bakdash & Marusich, 2017). Averaging the data from repeated measures for each participant prior to performing the correlation is a common method to resolve the issue of non-independence; however, this can produce misleading results if there are meaningful differences between different data points (Bakdash & Marusich, 2017). In the primary study, the pain scores (i.e., NWps, PIPP-R, the four-item NFCS) before, during and after painful and non-painful procedures did have meaningful differences in the three different phases of procedures (Hu, Harrold, et al., 2019). Thus, the correlations of the average pain scores were not analyzed but the correlations of NWps with PIPP-R and the four-item NFCS at different phases of procedures were analyzed and reported separately.

Diagnostic test accuracy

Diagnostic tests are widely used by HCPs to identify the presence or absence of a condition in a patient for the purpose of developing an appropriate treatment plan (The Joanna Briggs Institute, 2015b; White, Schultz, & Enuameh, 2011). Diagnostic test accuracy analysis aims to evaluate the accuracy of measurement of interest by comparing it to an existing referent measurement. In the primary study, the accuracy of NWps was evaluated by comparing it to PIPP-R for identifying the presence or absence of moderate to severe pain in mechanically ventilated infants (Hu, Harrold, et al., 2019). The definition of moderate to severe pain was defined as a PIPP-R greater than or equal to 13 (Stevens et al., 2014; Stevens et al., 1996).

The excellent level of mean and 95% confidence interval of area under ROC showed that SC, generally, had an excellent degree of the discriminative power of SC for pain measurement in mechanically ventilated infants. Specifically, the cut-off point of 0.235 of NWps was identified as having the highest Youden's index. This cut-off point of NWps resulted in low likelihood ratio for negative test results and high likelihood ratio for positive test results. The low likelihood ratio for negative test result indicated that negative SC results occurred more often in infants without moderate or severe pain than those with moderate or severe pain and provided convincing ruling-out discriminative accuracy of SC for pain measurement in mechanically ventilated infants. The high likelihood ratio for positive test result indicated that positive SC results occurred more often in infants with moderate or severe pain than those without moderate or severe pain and provided convincing ruling-in discriminative accuracy.

This cut-off point of NWps also resulted in the excellent specificity, sensitivity, and negative predictive value, but only sufficient positive predictive value. These findings indicated that few infants without moderate or severe pain (i.e., PIPP-R<13) had incorrectly positive SC results (i.e., NWps≥0.235); few infants with moderate or severe pain had incorrectly negative SC results; few infants, who had negative SC results, were false negative cases and truly with moderate or severe pain; but one-third of infants, who had positive SC results, were false positive cases and truly without moderate or severe pain.

In conclusion, the low likelihood ratio for the negative test result and the excellent specificity and negative predictive value indicated that SC was able to detect an infant without moderate to severe pain based on the negative SC result (i.e., NWps<0.235). The high likelihood ratio for the positive test result and excellent sensitivity indicated that SC was able to detect an infant with moderate to severe pain based on the positive SC result. However, the positive predictive value did not reach an excellent level and indicated that one-third of infants, who had positive results, were incorrectly considered as having moderate to severe pain and could be over-treated if they received pain treatments based on SC results.

The diagnostic test accuracy analysis provides more information on validity evidence than correlation or statistical regression methods (Buntinx & Knottnerus, 2009). This analysis has also been widely used in the studies of validating SC for pain measurement in older children (Choo et al., 2010; Hullett et al., 2009) and adults (Ledowski et al., 2011; Ledowski, Ang, et al., 2009; Ledowski et al., 2006; Ledowski, Bromilow, et al., 2007; Ledowski, Preuss, et al., 2007; Ledowski, Preuss, et al., 2009; Storm, Shafiei, Myre, & Raeder, 2005). However, only one of the 23 published studies, which evaluated the validity evidence of SC in relation

to referent pain measures, conducted diagnostic test accuracy analysis (Dalal et al., 2013). Dalal and colleagues tested the accuracy of NWps for identifying the presence or absence of discriminating moderate to severe pain, which was compared with nine-item NFCS that was scored greater than or equal to 4 out of 9 points. The results showed that the cut-off point of NWps was 0.571 for discriminating moderate to severe pain (Dalal et al., 2013). It was also reported that this cut-off point had a sensitivity of 54.5%, a specificity of 79.4%, a positive predictive value of 21.4%, and a negative predictive value of 94.4% (Dalal et al., 2013). The good specificity and excellent negative predictive value indicated that SC was able to detect an infant without moderate to severe pain based on the negative SC result (i.e., NWps<0.571). Especially, the excellent negative predictive value gives healthcare professionals high confidence that if SC is negative for pain measurement in an infant, there will be only 5.6% of probability that the infant will be incorrectly considered as having moderate to severe pain in the study. However, the poor sensitivity in the study indicated that only 54.5% of infants with moderate or severe pain had a positive SC result (i.e., NWps≥0.571). In addition, the poor positive predictive value in the study indicated that 78.6% of the positive results from the SC measures were false positive values. Thus, around half of the infants with moderate or severe pain could not be identified, and around three fourth of infants, who had positive results, were incorrectly considered as having moderate to severe pain.

Compared to the Dalal et al., (2013) study, the cut-off point in the primary study (Hu, Harrold, et al., 2019) was much lower, and the outcomes of diagnostic test accuracy analysis had better performance on discriminating moderate to severe pain in infants. The difference

might be due to different populations, pain construct, and context. In Dalal et al., (2013) study, SC was tested in infants aging from six to 12 months for measuring acute postoperative pain for 1 hour following arrival to the post-anesthesia care unit (PACU) (Dalal et al., 2013). In the primary study, SC was tested in mechanically ventilated infants aged from newborns to 12 months for measuring acute procedural pain in the NICU and PICU (Hu, Harrold, et al., 2019). However, it is difficult to make the judgment that SC showed different accuracies for measuring acute prolonged pain (i.e., postoperative pain) and acute procedural pain in these different infant populations. First, these two studies used different referent pain measurements, which were PIPP-R in the primary study (Hu, Harrold, et al., 2019) and the nine-item NFCS in the Dalal et al., (2013) study. Dalal et al., (2013) did not provide a reference to support their cut-off point of NFCS for measuring moderate to severe pain, and there is no evidence of cut-off points of NFCS and especially the four-item NFCS subset for different levels of pain intensity. Thus, the primary study did not compare SC to the four-item NFCS subset (Hu, Harrold, et al., 2019). Second, the difference is probably due to the different SC calculation and sampling methods, although the same Med-Storm SC device was used in both studies. In Dalal et al., (2013), the time window for obtaining NWps and observation time interval were set at 5 seconds and 15 minutes respectively, which were different from the primary study (Hu, Harrold, et al., 2019). In addition, the SC sampling method was not reported.

SC calculation and sampling

Using various SC calculation methods is also a common issue across the previous

studies validating or using SC for pain measurement in infants. The refreshing time of Med-Storm SC device is one second, which means a new NWps value is obtained every second (Med-Storm Innovation AS, 2012). In addition, NWps is the number of waves in a time window divided by the time span of the window (Med-Storm Innovation AS, 2012). Thus, it is important to report the NWps calculation and sampling methods. However, only ten of the 32 previous studies reported the time window of calculating NWps (Baleine et al., 2014; Cresi et al., 2012; Dalal et al., 2013; de Jesus et al., 2015; de Jesus, Tristao, Storm, da Rocha, & Campos, 2011; Lyngstad et al., 2014; Munsters et al., 2012; Scaramuzzo et al., 2013; Valkenburg et al., 2012; van der Lee et al., 2015), and only six of these ten studies used the 15 seconds time window (Baleine et al., 2014; de Jesus et al., 2015; de Jesus et al., 2011; Lyngstad et al., 2014; Scaramuzzo et al., 2013; van der Lee et al., 2015). In the primary study (Hu, Harrold, et al., 2019), the 15 seconds time window was used to calculate NWps, based on previous studies and the Med-Storm SC product manual, which recommended this as an appropriate time frame (Choo et al., 2010; Ledowski et al., 2011; Med-Storm Innovation AS, 2012). Most studies included in the scoping review reported SC observation time intervals for pain measurement in infants, but these varied from 20 minutes prior to procedures to 60 minutes following arrival to the PACU (Hu, Modanloo, et al., 2019). The primary study used 30 seconds observation time intervals, which were the same 30 seconds observation time intervals as PIPP-R and the four-item NFCS, before, during, and following completion of the procedure (Hu, Harrold, et al., 2019).

The results of the scoping review (Hu, Modanloo, et al., 2019) showed that only one study reported the SC value sampling method, which was used to obtain a SC value during a

specific observation time interval (Lyngstad et al., 2014). Lyngstad et al.'s study reported using the maximum SC value 5 minutes before, during and 5 minutes after a diaper change (Lyngstad et al., 2014). The maximal value of NWps, which was measured in the 30 seconds observation time interval, was extracted in the primary study (Hu, Harrold, et al., 2019). Using the maximal value of NWps was compatible with the scoring systems of PIPP-R and the four-item NFCS, which capture the maximal intensity of facial expression, highest heart rate, and lowest oxygen saturation (Grunau & Craig, 1987; Stevens et al., 2014).

Validity evidence in relation to other variables

Validity evidence is not intrinsic to the measure but an interaction between the tool, the population to which it is applied and the context under which it is applied (American Educational Research Association, 2014). Thus, the primary study collected demographic and medical information from each included infant (Hu, Harrold, et al., 2019). Although the purpose of the primary study was not to identify the potential factors influencing SC, the relationships between SC, and four demographic and nine medical variables were also analyzed in the primary study as secondary outcomes (Hu, Harrold, et al., 2019). The four demographic variables included gestational age, postnatal age, current weight and sex, and the nine medical variables included diagnosis, number of days in NICU or PICU, mechanical ventilation mode, number of days on ventilation, NTISS scores (i.e., severity of illness), type of painful procedures, type of non-painful procedures time length between painful and non-painful procedures, administration of oral sweet solution prior to painful procedures, and use of analgesics or sedatives administered within the 6 hours before observation. However, no

statistically significant relationships were found in the primary study (Hu, Harrold, et al., 2019). The results in the scoping review showed that the associations of SC with four demographic and nine medical variables were tested in 21 studies (Hu, Modanloo, et al., 2019). The four demographic variables were the same to those in the primary study (Hu, Harrold, et al., 2019). In terms of medical variables in these 21 studies, only two were same as those in the primary study, which were the administration of oral sweet solution prior to painful procedures and severity of illness (Hu, Harrold, et al., 2019). In the scoping review, no statistically significant relationships were found between SC and most of the variables, such as birth delivery method, skin or environment temperature, current weight, number of previous blood sampling procedures and severity of illness (Hu, Modanloo, et al., 2019).

In the scoping review (Hu, Modanloo, et al., 2019), seven studies examined the association between sex and SC (de Jesus et al., 2015; de Jesus et al., 2011; Eriksson et al., 2008; Hernes et al., 2002; Pereira-da-Silva et al., 2012; Salavitabar et al., 2010; Schubach et al., 2016). Differences in SC between male and female infants were only found in two studies (Pereira-da-Silva et al., 2012; Salavitabar et al., 2010). Salavitabar et al. (2010) showed female infants had statistically significantly higher NWps compared to male infants using independent sample t test (Salavitabar et al., 2010), but Pereira-da-Silva et al. (2012) reported the opposite findings using multivariate logistic regression analysis (Pereira-da-Silva et al., 2012). Infants who had gastroesophageal reflux (Cresi et al., 2012) had statistically significantly higher NWps than those who without gastroesophageal reflux. Both Schubach et al., (2016) and Oji-Mmuo et al., (2019) found that neonates exposed to opioids in utero had statistically significantly higher NWps than those who were not exposed to opioids in utero

(Oji-Mmuo et al., 2019; Schubach et al., 2016).

The associations between SC and gestational age were tested in ten studies, and the associations between SC and postnatal age were tested in nine studies. Statistically significant relationships between SC and gestational age (Gladman & Chiswick, 1990; Hellerud & Storm, 2002) and postnatal age (Hellerud & Storm, 2002; Storm, 2000) were found in only two studies respectively, accounting for less than 20% of the total studies on validity evidence of SC in relation to gestational age or postnatal age, which were included in the scoping review (Hu, Modanloo, et al., 2019). One recently published study assessed the effect of prematurity at term-equivalent age on SC during hip dysplasia screening, compared to healthy full-term infants (Maillard et al., 2019). The study findings were conflicting: preterm infants at term-equivalent age exhibited statistically significantly lower basal NWps compared to healthy full-term infants, but non-statistically significantly different NWps during the stimulus and NWps increase from baseline to during stimulus (Maillard et al., 2019). Thus, it is difficult to draw conclusions on the relationships of SC with gestational age or postnatal age.

Pain treatments (e.g. analgesics, skin-to-skin contact, oral sweet solution) are one of the most important contexts in SC validation studies. The validity of SC in relation to pain treatments is important as a valid pain measurement should be able to detect a change in pain due to implemented known effective pain treatments. The validity evidence of SC in relation to pain treatment was tested in five previous studies, including the validity of SC in relation to skin-to-skin contact in one study (Lyngstad et al., 2014), and the validity of SC in relation to oral sweet solution (i.e., sucrose or glucose) in four studies (Beken et al., 2014; Munsters

et al., 2012; Passariello et al., 2019; Storm & Fremming, 2002). In Lyngstad et al., (2014) study, which was included in the scoping review (Hu, Modanloo, et al., 2019), the mothers provided skin-to-skin care by holding her hands at the infants head and body in lateral kangaroo position. The results of this study showed that skin-to-skin contact did lead to a significantly lower SC in infants during diaper change compared to laying in incubators or cots (Lyngstad et al., 2014). In two studies in the scoping review (Hu, Modanloo, et al., 2019), SC was used to measure the effect of oral sucrose on pain relief in infants during heel lance (Storm & Fremming, 2002) and the effect of oral glucose on pain relief in infants during venipunture (Beken et al., 2014). However, NWps did not differ in infants receiving oral sweet solution compared to water (Beken et al., 2014; Storm & Fremming, 2002). In addition, Munsters et al., (2012) did not identify a statistically significant decrease in SC after the administration of oral glucose. One of the reasons may have been due to the small sample sizes (i.e., n=10 to 12) in these studies (Beken et al., 2014; Munsters et al., 2012; Storm & Fremming, 2002). In a more recently published study which was not included in the scoping review (Hu, Modanloo, et al., 2019), SC was used as the main outcome measuring the effect of oral sucorse on pain relief in infants during heel lance (Passariello et al., 2019). The sample size was estimated at 25 in each group based on 90% power to detect a reduction of at least 50% in NWps during heel lance in the infants receiving oral sucrose compared to those receiving water, when the probability of type I error was fixed at 5% (Passariello et al., 2019). The results showed that NWps during and three minutes after heel lance was lower in the sucrose group than the placebo group and that this difference was statistically significant (Passariello et al., 2019). However, there still remains a lack of strong evidence to support the

validity of SC in relation to pain treatments.

Contributions to existing knowledge

Infants are unable to give self-report, and they express their pain through behavioural and physiological cues (Cong et al., 2013; Lee & Stevens, 2014; Stevens et al., 2007; Stinson, 2009). HCPs report pain assessment as being more complex and difficult in infants than in older children and adults (Andersen, Nakstad, Jylli, Campbell-Yeo, & Anderzen-Carlsson, 2019; Cong et al., 2013; Hatfield & Ely, 2015; van Dijk & Tibboel, 2012). Infants are at increased risk for under recognition of pain compared with older children and adults (Andersen et al., 2019). The findings in this dissertation make significant contributions to the body of knowledge concerning infant acute pain and stress measurement.

To our knowledge, the scoping review is the first comprehensive review examining the use of SC for pain assessment in infants (Hu, Modanloo, et al., 2019). The validity evidence of SC for pain assessment in infants in relation to referent pain measures, stimulus, age, and other contextual variables was synthesized. In addition, the methods of evaluating the validity evidence of SC were also synthesized in the scoping review (Hu, Modanloo, et al., 2019). Although recommendations for the clinical use of SC in infant pain measurement could not be generated at this stage, these synthesized findings identified the inconsistent findings on validity evidence, common limitations across studies and key knowledge gaps in the field.

Although tremendous advances have been made in understanding pain responses, and more than six dozen pain measurement tools have been developed for infants (McGrath et al., 2014), an appropriate pain measurement tool for infants requiring mechanical ventilation is

still lacking due to the environment, patient conditions and medications (Stevens et al., 2007). SC is a novel and emerging approach to measuring pain in this vulnerable population; however, only one study had previously evaluated the validity of SC for pain assessment in mechanically ventilated infants (Karpe et al., 2013) and most previous studies included healthy newborns or medically stable hospitalized infants. The primary study focused on sick infants requiring mechanical ventilation, and added new knowledge on the validity of SC in relation to category of procedure and referent pain measures, and it also determined the cut-off point and diagnostic test accuracy of SC for identifying the mechanical ventilated infants having moderate to severe pain (i.e., PIPP-R ≥13) (Hu, Harrold, et al., 2019).

The primary study is the first study testing the different validity evidence of SC, which included relation to category of procedure (i.e., painful and non-painful), phase of procedure (i.e., before, during, after), and referent pain measures (i.e., PIPP-R and the four-item NFCS), in the same population during the same time period (Hu, Harrold, et al., 2019). These multiple comparisons in the same population of infants at the same time provided comprehensive validity evidence of SC for measuring pain in mechanically ventilated infants. This validity evaluation approach and the transparent reporting in the primary study (Hu, Harrold, et al., 2019) increased researcher and HCP confidence in the validity of SC and will facilitate the replication of the study. The primary study (Hu, Harrold, et al., 2019) could also contribute to the methodology development in the studies evaluating the validity of SC across different age groups.

Although more research is needed before SC can be recommended for clinical use in pain measurement, the findings in the primary study showed that SC is a promising approach

to measuring pain in in mechanically ventilated infants (Hu, Harrold, et al., 2019). SC provides a new approach for researchers and HCPs to understand the complexity of pain in infants. The scoping review (Hu, Modanloo, et al., 2019) and primary study (Hu, Harrold, et al., 2019) could raise awareness of this novel pain measurement to researchers and other potential knowledge users.

The AERA Standards are considered the best practice in the field of psychometrics and have also been commonly used in the field of health sciences (American Educational Research Association, 2014; Squires et al., 2015; Streiner, 2008), but it was the first time that the AERA Standards were used as a theoretical framework for examining the validity evidence of a pain measurement in infants. The concept of validity in the AERA Standards, which is heavily influenced by Messick's unitary view of validity (American Educational Research Association, 2014; Messick, 1995), provided a new perspective to the understanding of validity of infant pain measurements. It not only considers the findings obtained from traditional observational studies, which specifically aim for validating the SC as validity evidence, but also includes the findings from interventional studies, which use the SC as the pain outcomes.

Implications

The findings from our two studies (Hu, Harrold, et al., 2019; Hu, Modanloo, et al., 2019) have the following implications for clinical practice and research.

Implications for clinical practice

There has been a drive for objective indicators of measuring pain in infants (Berde &

McGrath, 2009; Raeside, 2011), as there are challenges in the use of subjective indicators of measuring infant pain in research and clinical practice. First, HCPs' assessment of pain in infants may be highly biased (Pronina & Rule, 2014; Tannous Elias, Dos Santos, & Guinsburg, 2014). Pain assessments may be affected by several confounding factors, such as the assessors' cognitive bias, knowledge, background, culture, and even gender (Pronina & Rule, 2014; Tannous Elias et al., 2014). To reduce bias, the need for more specialized training and better tools for assessing pain in infants is increasingly emphasized (Pillai Riddell et al., 2016). Second, HCPs assess pain at different time intervals and are not able to provide continuous pain assessment. Continuous monitoring is important, especially for critically ill infants, because they may experience pain between the pain assessment time intervals (Dale, Zhou, Zhang, Singh, & Wang, 2018; Zamzmi et al., 2018). Utilizing SC to measure pain in infants is more objective than using facial expressions or body movements especially in sick and preterm infants whose behavioural responses may be less obvious or unable to be assessed (Choo, 2013; Storm, 2008, 2013). The SC measurement device enables quick and straightforward measurement, requires a short training time, and the values of SC can be easily and quickly understood by clinicians and researchers. The findings in the primary study showed that SC is a promising approach to measuring pain in mechanically ventilated infants (Hu, Harrold, et al., 2019). Thus, SC has potential as a routine clinically useful measure of pain and as an outcome evaluating the effectiveness of pain treatments in critically infants, who require painful procedures as part of their nursing and medical care.

However, the values of SC must be used with caution when making clinical decisions about pain treatment in mechanically ventilated infants, due to the imperfect correlations with

the referent pain measures and imperfect positive predictive value. The underlying mechanism of these different pain assessment methods in infants is based on how nociceptive stimulation alters infant responses across all levels of the peripheral and central nervous system in the nociception pathway (Fitzgerald & Walker, 2009). Thus, a multi-modal pain measurement approach, using different pain measurement methods at the same time, is recommended to understand the complexity of pain in infants (Pillai Riddell et al., 2016; Roue et al., 2018; Worley, Fabrizi, Boyd, & Slater, 2012). SC may be best used along with other pain scales, for example, PIPP-R and the four-item NFCS, as these scales provided a different dimension of pain in infants from SC and may exclude false positive cases compared to when only using SC. Additionally, it is also important to interpret infant pain responses as a dynamic interplay between biological, psychological, and social determinants of pain (Hadjistavropoulos & Craig, 2002; van Dijk & Tibboel, 2012). Pain measurement using SC needs to be considered along with the status of the individual infant, personal expression, and pain-related contextual factors (Craig, 2015; Fuller, 1998; Schiavenato & Craig, 2010).

Implications for research

The validity of SC for acute pain measurement in relation to pain treatment is important as a valid pain measurement should be able to detect a change in pain due to pain treatments (Berde & McGrath, 2009; Registered Nurses' Association of Ontario, 2013). An analysis in the primary study explored the association of SC with analgesics (e.g., fentanyl, morphine, sucrose) (Hu, Harrold, et al., 2019). However, the sample size was not estimated based on

this analysis. In addition, no previous study has evaluated validity evidence of SC in relation to analgesics. Thus, SC as a measurement of pain in mechanically ventilated infants in this context needs to be evaluated in future studies. It is also recommended that SC should be used as an outcome measure in addition to behavioural pain scales to evaluate the effectiveness of pain treatments in critically ill infants.

Studies to answer questions about the impact of introducing SC as a pain assessment tool on pain treatment and patient outcomes would provide additional insight into the issues of using SC for pain measurement in infants. In clinical practice, it is not helpful to implement pain measurement as a stand-alone procedure (van Dijk & Tibboel, 2012). It is important to establish the linkage of SC values to pain treatment, for example, how SC could guide the increase or decrease in the amount of administered analgesics. It is also important to evaluate whether using SC as the measure of pain makes a difference in the dosing of analgesics. Additionally, HCP and parent perceptions related to using SC alone or with other pain measurement methods need to be studied.

In the scoping review, inconsistent findings on the validity of SC was found (Hu, Modanloo, et al., 2019). Some of the inconsistent findings can potentially be explained by differences in the methods of validating SC for pain measurement in infants in different studies. Varied methods were evident across the studies including hypothesis testing, sample size, the collection of demographic and medical information, selection of painful and non-painful procedures, sequence of painful and non-painful procedures, preparation time length before procedures, time interval between painful and non-painful procedures, choice of referent pain measures, positivity cut-offs or result categories of the referent pain measures,

data analysis methods, and SC calculation and sampling. These issues also exist in studies validating or using cardiovascular indices (e.g., heart rate, heart rate variability) for acute pain responses in infants (Waxman et al., 2016). To address these issues, the methodology quality criteria or reporting standards for the studies of using cardiovascular indices were recommended (Constantin, Bailey, & McMurtry, 2018; Laborde, Mosley, & Thayer, 2017). Thus, it is warranted that methodology quality criteria or reporting standards need to be developed in the studies of validating or using SC for pain measurement. The criteria of cross-sectional studies, such as Estabrooks' Quality Assessment and Validity Tool and the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) (Estabrooks, Floyd, Scott-Findlay, O'Leary, & Gushta, 2003; Vandenbroucke et al., 2007), and the criteria of diagnostic test accuracy studies, such as the updated Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2), the updated Standards for Reporting Studies of Diagnostic Accuracy (2015 STARD) (Bossuyt et al., 2015; Whiting et al., 2011) could be foundational to developing these recommendations.

The SC measurement device from Med-Storm Innovations was used in the primary study (Hu, Harrold, et al., 2019) and is the most commonly used device in the previously published 32 studies. The Med-Storm SC product manual provided detailed information on the apparatus preparation, electrodes placement and software setup (Med-Storm Innovation AS, 2012). However, few studies reported the operating mechanism and validity and reliability of the device from Med-Storm Innovations measuring SC, which could introduce test bias across studies. Thus, it is important for the Med-Storm Innovations company to provide more detailed information on the Med-Storm SC measurement device's operating

mechanism and validity and reliability of measuring SC.

The results in the scoping review (Hu, Modanloo, et al., 2019) showed that twelve of the 28 included studies, which involved a total of 293 infants, reported reasons for missing data (Baleine et al., 2014; Cresi et al., 2012; Dalal et al., 2013; de Jesus et al., 2015; de Jesus et al., 2011; Eriksson et al., 2008; Harrison et al., 2006; Hernes et al., 2002; Lyngstad et al., 2014; Roeggen, Storm, & Harrison, 2011; Schubach et al., 2016; van der Lee et al., 2015), all of which were due to technical issues of the SC measurement device or electrodes (n of infants=27, 10%) leading to recording loss (n=7), low quality of measured SC (n=9), collection failure (n=10) and electrodes not secured to the skin (n=1). In the primary study (Hu, Harrold, et al., 2019), there were technical problems resulting in missing data for seven infants (13%). These technical issues of the SC measurement might be a negative factor influencing the use of SC device as monitor for assessing infant pain continuously for 24 hours in clinical settings. Thus, translational research using an interdisciplinary collaborative approach between technologists and pain scientists is warranted to advance the technology of measuring SC and then reduce the mechanical failures.

The primary study only evaluated the validity of SC for pain measurement using NWps as the parameter of SC (Hu, Harrold, et al., 2019). In addition, NWps has been illustrated to be the most accurate SC parameter for pain measurement in infants, children and adults (Macko et al., 2014; Storm, 2008, 2013; Valkenburg et al., 2012) and was the most commonly used parameter for measuring pain in infants in previous studies, which were included in the scoping review (Hu, Modanloo, et al., 2019) or published after the competition of the scoping review (Hu, Modanloo, et al., 2019; Maillard et al., 2019; Oji-Mmuo et al., 2019; Passariello

et al., 2019; Roue et al., 2018). However, Pereira-da-Silva et al (2012) found that NWps was not significantly different but the SC parameters area small peaks and average rise time were significantly different when heel lance was used to draw blood for gas analysis compared with when it was used for glycaemia. The authors suggested that larger area under the small peaks (bigger area small peaks value) and swifter SC rises (smaller average rise time value) could indicate that the sympathetic nervous system is firing more forcefully and suggest a more intense stimulus, as heel lance for gas analysis requires collecting a larger volume of blood for a longer period than for the very small amount of blood required for glycaemic testing (Pereira-da-Silva et al., 2012). Thus, secondary data analysis studies based on the primary study (Hu, Harrold, et al., 2019) will be conducted to explore the validity of different SC parameters for measuring pain in mechanically ventilated infants.

In the primary study (Hu, Harrold, et al., 2019) and previous studies, a SC value at one time point during a period of time was always sampled and extracted to represent the pain intensity during the period of time. For example, the primary study used the maximal value of NWps which was measured in the 30 seconds observation time interval (Hu, Harrold, et al., 2019). The limitation of this sampling approach is that it excludes the other data during the time interval and ignores the changes and trends. In the past several years, progressions in artificial intelligence and machine learning science have made the analysis of big data accessible to researchers and HCPs (Zamzmi et al., 2018). There has been increasing interest in the use of computer science for understanding human behavioural responses to pain based on the analysis of facial expressions, crying, and body movements (Zamzmi et al., 2018). Thus, interdisciplinary research involving pain scientists, HCPs and computer scientists is

important to advance the technology of analyzing SC, which will include more data from different SC parameters and in a longer period of time with continuous data points.

Limitations

Three key limitations to Study One, the scoping review were identified (Hu, Modanloo, et al., 2019). First, the literature search in this scoping review was restricted to studies only published in English. Second, frequencies rather than any further synthesis methods were used in the scoping review to describe the evidence due to heterogeneous study designs, including populations, settings and statistical methods. Finally, the weight of evidence and recommendations were not developed as there were no appropriate standards available to demonstrate whether the evidence is sufficient to support the validity evidence of SC.

There were three key limitations to Study Two, the primary study (Hu, Harrold, et al., 2019). First, this study was an observational study, and there was no attempt to standardize painful or non-painful procedures and pain treatments. Potential influencing variables in mechanically ventilated infants during data collection were not controlled, although dependent group statistics were used in this study to ensure that the pair of data was from the same patient during the same period of time and in the same context. Second, due to the absence of a gold standard for pain measurement in infants, multiple surrogate approaches were used to evaluate the validity evidence of SC for pain measurement in our study. These approaches were based on the assumptions that skin-breaking procedures and traumatic procedures are painful, and diaper change, along with abdominal circumference measurement, temperature measurement, or lung auscultation, is stressful but not painful, and

the scores of PIPP-R and four-item NFCS showed good validity in infant pain measures. However, these assumptions could be challenged, as skin-breaking procedures and traumatic procedures might lead to distress rather than pain in infants; tactile stimuli might be painful to infants, especially preterm infants; and the ability of PIPP-R and four-item NFCS to distinguish pain from distress is questioned. Third, the observation of painful or non-painful procedures was separated into baseline: the first 30 seconds in the three minutes prior to procedure; during procedure: the first 30 seconds following procedure, and recovery: the last 30 seconds in the three minutes after completion of procedure. The separation of these 30 seconds observation periods ensured the included infants were less likely to be handled for preparation before the procedure or settling after the procedure during these periods of observation. Thus, the data collected during these time windows would be more likely to represent the infant's conditions during baseline and recovery. However, the duration of this separation was arbitrarily set a priori.

Knowledge dissemination

Different knowledge dissemination activities have been implemented to target our research findings to specific audiences. As our research is at the early stages of discovery and the new findings have more relevance to the academic audience, the goals of our knowledge dissemination are to share knowledge with different potential knowledge users and raise awareness of knowledge to them.

A one-page pamphlet (Appendix P), which summarizes our research findings, was emailed to the nurses, physicians and leaders in the NICU and PICU at CHEO for

dissemination. The summary was also posted in different places in the NICU and PICU for reading, which included unit research whiteboards, nursing stations, staff offices, and staff rooms. This one-page pamphlet was adapted to parent version (Appendix Q), and it was sent to the parents who provided their emails or mailing addresses to receive a summary of the findings. Copies of this one-page summary (parent version) were also placed in the parent education area and family rest rooms in the NICU and PICU so that parents could obtain and read the summary of the findings. The preliminary findings of the primary study (Hu, Harrold, et al., 2019) were also presented at a CHEO nursing research conference (Ottawa, Canada) to the nurses and investigators and CHEO NICU research rounds (Ottawa, Canada) to the physicians and nurses.

The scoping review has been published by the Clinical Journal of Pain (Hu, Modanloo, et al., 2019), and the primary study has been submitted to Pain, the official journal of the International Association for the Study of Pain (Hu, Harrold, et al., 2019). These publications mainly target researchers. In addition, oral and poster presentations were given in conferences to researchers and HCPs. The findings of the scoping review (Hu, Modanloo, et al., 2019) were presented at the International Scientific Meeting at Connaught Summer Institute in Pain (Toronto, Canada) and 11th International Symposium on Pediatric Pain (Kuala Lumpur, Malaysia). The findings of the primary study (Hu, Harrold, et al., 2019) were presented at the International Association for the Study of Pain World Congress on Pain (Boston, USA) and Canadian Pain Society 40th Annual Scientific Meeting (Toronto, Canada). Lastly, the preliminary findings of the primary study (Hu, Harrold, et al., 2019) were respectively presented through Webinars in the Pain in Child Health (PICH) community, which is a

Canadian Institutes of Health Research strategic training initiative.

As the primary study (Hu, Harrold, et al., 2019) was supported by the Sigma Theta Tau International/Rosemary Berkel Crisp Research Award (2018-2019), a study report was sent to the funder and also uploaded to Virginia Henderson Global Nursing e-Repository (Henderson Repository) as grey literature, which is freely open to the public. Additionally, the final version of this thesis will be uploaded to the University of Ottawa's digital repository for research and teaching materials, which provides open and permanent access to the University of Ottawa's scholarship and ensures its wide dissemination and increased visibility online. To disseminate our research findings to the public, a plain summary was sent to CBC Radio for the column of “Ideas from the Trenches.” However, up to now, no feedback from CBC Radio has been received.

Conclusions

This dissertation consists of two studies and provides insight on the validity of SC for measuring pain in infants. The findings in the scoping review (Hu, Modanloo, et al., 2019) revealed the current methods and findings on evaluating the validity evidence of SC for measuring acute pain in infants across the studies, identified the inconsistent findings on validity evidence, common limitations across studies and key knowledge gaps in the field, and led to the objectives, population, and methods in the primary study. The findings of the primary study (Hu, Harrold, et al., 2019) demonstrated that SC showed good validity in relation to category of procedure (painful compared to non-painful), phase of painful or non-painful procedure (before, during and after), and two referent pain measures (PIPP-R and the

four-item NFCS) with respect to pain measurement in mechanically ventilated infants. The primary study also determined the cut-off point and diagnostic test accuracy of SC for identifying the mechanical ventilated infants having moderate to severe pain (i.e., PIPP-R≥13). In addition, the AERA standards provide a useful framework for synthesizing the established sources of validity evidence, as well as for conducting multiple comparisons to develop comprehensive validity of SC for pain measurement in infants.

The findings from this dissertation have significant implications for clinical practice and research. The values of SC must be interpreted with caution for pain measurement in infants and along with the status of the individual infant, personal expression, and pain-related contextual factors. Further research testing the validity of SC in relation to pain treatments and advancing the technology of measuring and analyzing SC is warranted.

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Chapter 5: Contributions of Collaborators

This chapter specifies the primary researcher and each collaborator's distinct contribution to this doctoral dissertation and published papers and/or manuscripts included in the dissertation. Decisions around authorship were made in accordance with the International Committee of Medical Journal Editors (2018) and the Faculty of Graduate and Postdoctoral Studies at the University of Ottawa (2018). This chapter also contains acknowledgments for research personnel who supported some aspects of the two studies. A detailed account of member contributions is listed in Table 4-1.

Primary researcher and thesis committee

Primary Researcher

This dissertation is the original work of the PhD candidate Jiale Hu (J. Hu). Specifically, the candidate led and was engaged in all aspects of the two studies as part of the fulfillment of the requirements of the degree of Doctorate of Nursing at the University of Ottawa, including the conceptualization and design of the studies, literature searching and screening, patient recruitment, data collection, data analysis, interpretation of findings and manuscript preparation. The candidate accepts full responsibility for each manuscript and the dissertation as a whole.

The doctoral studies of the candidate were financially supported by the Ontario Trillium Scholarship (2015-2019) and International Doctoral Scholarship from the University of Ottawa (2018-2019). Study Two was funded by the Sigma Theta Tau International/Rosemary Berkel Crisp Research Award (2018-2019) and Canadian Pain Society Trainee Research

Award (Clinical Science, 2018-2019); none of which had a role in study design, data collection and analysis, publication decisions, or preparation of the manuscripts or dissertation.

Thesis Committee

The two studies and this doctoral dissertation were conceived in collaboration with the candidate's supervisor Dr. Denise Harrison, RN, PhD (DH), and committee members, Dr. Janet Squires, RN, PhD (JS) and Dr. JoAnn Harrold, MD, FRCPC (J. Harrold). DH is a Professor in the School of Nursing, University of Ottawa and the Chair in Nursing Care of Children, Youth and Families at Children's Hospital of Eastern Ontario (CHEO), Ontario, Canada. JS is a Professor in the School of Nursing, University of Ottawa and a Scientist in Clinical Epidemiology, Ottawa Hospital Research Institute, Ontario, Canada. J. Harrold is an Associate Professor in the Faculty of Medicine, University of Ottawa and Chief of Neonatology at CHEO and the Ottawa Hospital, Ottawa, Ontario. All these three main collaborators provided significant contributions to the design of the research and approved the research proposal. They also provided conceptual and methodological support throughout this scholarly work, participated in the analysis and interpretation of data, critically reviewed and edited each manuscript and the dissertation, approved the final version of the work to be published, and had agreement on the integrity and accuracy of the work.

Other Collaborators and Acknowledgements

There was one additional collaborator, who met the International Committee of Medical Journal Editors guideline for authorship on two manuscripts in the dissertation. Ms.

Shokoufeh Modanloo, RN, MScN (SM) is a PhD Candidate in the School of Nursing, University of Ottawa, Ontario, Canada. In Study One, SM was the second reviewer for the title/abstract and full-text screening and data extraction. In Study Two, SM participated in patient screening, data collection, and video coding. She also provided feedback on analyzing and interpreting the data, contributed intellectual content, and critically reviewed and approved the final version of the two manuscripts.

The candidate acknowledges the contributions of Marie-Cécile Domecq (MCD), Margaret Sampson (MS), Franco Momoli (FM), and Juliana Choueiry (JC). MCD is a librarian at University of Ottawa and MS is a librarian at Children's Hospital of Eastern Ontario (CHEO). They facilitated the process of searching for the articles and helped to check the search terms and databases in Study One. FM is an associate scientist at Clinical Epidemiology Program, Ottawa Hospital Research Institute and a scientist at CHEO Research Institute. He provided consultation to the analysis and interpretation of the data in Study Two. JC is an undergraduate nursing student at University of Ottawa. She coded the videos independently and discussed the discrepancies with J. Hu and SM in Study Two. Thanks are also due to the nurses and physicians in the NICU and PICU at CHEO located in Ottawa, Canada and all parents who agreed to participate.

Reference

International Committee of Medical Journal Editors (2018). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Retrieved March 10, 2019, from http://www.icmje.org/recommendations/

Faculty of Graduate and Postdoctoral Studies at the University of Ottawa (2018). Preparing a thesis or a research paper at the University of Ottawa. Retrieved March 10, 2019, from https://www.uottawa.ca/graduate-studies/students/theses

Table 5- 1. Contribution of collaborators for submitted articles

Element	Chapter 2 (Published)	Chapter 3 (Submitted)
Title	The Validity of Skin Conductance for Assessing Acute Pain in Infants: A Scoping Review	The Validity of Skin Conductance for Measuring Pain in Mechanically Ventilated Infants
Conceptualization and design	J. Hu DH JS J. Harrold	J. Hu DH JS J. Harrold
Data collection	J. Hu DH SM MCD MS	J. Hu DH J. Harrold SM JC
Data analysis and interpretation	J. Hu DH SM	J. Hu DH FM SM
Draft manuscript	J. Hu	J. Hu
Manuscript revisions for	J. Hu	J. Hu

important intellectual content	DH JS J. Harrold SM	DH JS J. Harrold SM
Approval of final version for publication	J. Hu DH JS J. Harrold SM	J. Hu DH JS J. Harrold SM
Responsible for overall content	J. Hu	J. Hu

Appendices

Appendix A. Ethic Certificates and Renewal

REB Protocol No 17/85X Final Approval - Delegated Review
vbourada@cheo.on.ca
Sent: August-23-17 10:30 AM
To: Hu, Jiale
Cc: Harrison, Denise; Ledoux, Sheila; Bourada, Valerie

CHEO Research Ethics Board
Approval - Delegated Review

Principal Investigator: Mr. Jiale Hu
REB Protocol No: 17/85X
Romeo File No: 20170268
Project Title: CHEOREB# 17/85X - Validating Skin Conductance for Assessing Pain and Stress in Mechanically Ventilated Infants
Primary Affiliation: Clinical Research\Nursing
Protocol Status: Active
Approval Date*: August 23, 2017
Valid Until:** May 15, 2018
Annual Renewal Submission Deadline: 15 April 2018
Please note that approval is contingent on the receipt and use of the research label on the pain monitor for use in this study.

Documents Reviewed & Approved:

Document Name	Comments	Version Date
Investigator Response	Itemized response letter signed by the PI	2017/08/17
Protocol	Modified20170817, SC for ventilation Protocol	2017/08/17
Other Document	SC Appendix A-Eligibility Checklist, 20170502	2017/05/02
Recruitment Materials	Modified20170817, SC Appendix B-Recruitment Poster	2017/08/17
Consent Form	Modified20170817, SC Appendix C-Parent Information and Consent Form	2017/08/17
Consent Form	Modified20170817, SC Appendix D-Media Records Release Form	2017/08/17
Case Report Form	SC Appendix E-Data Collection Form I, 20170502	2017/05/02
Other Document	SC Appendix F-NTISS Scoring System, 20170502	2017/05/02
Case Report Form	SC Appendix G-Data Collection Form II, 20170502	2017/05/02
Case Report Form	SC Appendix H-Adverse Event Report Form, 20170502	2017/05/02
Other Document	SC Appendix I-PIPPR Scale, 20170502	2017/05/02
Other Document	SC Appendix J-COMFORT-B Scale, 20170502	2017/05/02
Other Document	SC Appendix K-NFCS Scale, 20170502	2017/05/02

This is to notify you that the Children's Hospital of Eastern Ontario Research Ethics Board has granted approval to the above named research study on the date noted above. Your project was reviewed under the delegated review stream, which is reserved for projects that involve no more than minimal risk to human subjects.

Final approval is granted for the above noted study, with the understanding that the investigator agrees to comply with the following requirements:

1. The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.
2. The investigator is responsible for complying with all applicable guidelines and regulations regarding human research ethics conduct, as applicable to the research project.
3. Approval for studies that include an investigational device(s) is contingent upon the investigator securing an Investigational Testing Authorization notice from Health Canada.
4. Investigators must submit an annual renewal report to the REB 30 days prior to the expiration date stated above.
5. The investigator must not implement any deviation from, or changes to, the protocol, consents or assents without the approval of the REB.
6. The investigator must, prior to use, submit to the Board changes to the study documentation, e.g., changes to the informed consent letters, recruitment materials.
7. Investigators must provide the Board with French versions of the consent form, unless a waiver has been granted. An interpreter should be offered to participants as required or at the request of the participant throughout the course of research.
8. The investigator must promptly report to the REB all unexpected and untoward occurrences (including the loss or theft of study data and other such privacy breaches).
9. Investigators must notify the REB of any study closures (closed to accrual, temporary, premature or permanent).
10. Investigators must submit a final report at the conclusion of the study.

Should you have any questions or concerns, please do not hesitate to contact the Research Ethics Board Office at 613-737-7600 ext. 3350 or 2128.

Regards,

Richard Carpentier, PhD
Chair, Research Ethics Board
Président, Comité d'éthique de la recherche

*The final approval date for initial delegated study applications approved with or without modifications will be the date the REB has determined that the conditions of approval have been satisfied.

**The expiry date of REB approval for initial study application that required no modifications will be as follows:
• If the date of review and approval was **on or before** the 15th of the month, the expiry date will be the 15th of the month prior to the date of review and approval by the Chair and/or delegate *in the following year*;
• If the date of review and approval was **after** the 15th the expiry date will be the 15th of the month in which the date of review and approval by the REB *in the following year*.

The expiry date of REB approval for initial study applications that **require modifications** will be as follows:
• If the initial feedback was sent **on or before** the 15th of the month, the expiry date will be the 15th of the month prior to the date the letter of REB feedback is issued to the investigator(s) *in the following year*;
• If the initial feedback was sent **after** the 15th the expiry date will be the 15th of the month in which the feedback was sent *in the following year*.

RESEARCH INSTITUTE
INSTITUT DE RECHERCHE

Research Ethics Board
2018 Annual Renewal (Delegated)

Principal Investigator: Mr. Jiale Hu
REB Protocol No: 17/85X
Romeo File No: 20170268
Project Title: CHEOREB# 17/85X - Validating Skin Conductance for Assessing Pain and Stress in Mechanically Ventilated Infants
Primary Affiliation: Clinical Research\Nursing
Protocol Status: Active
Approval Date: April 17, 2018
Approval Valid Until: May 15, 2019
Annual Renewal Submission Deadline: April 15, 2019
This is to notify you that the CHEO REB has granted approval to the renewal for the above named research study for a period of one year. The renewal was reviewed and approved by the Chair or a delegate of the Chair. Decisions made by the Chair under delegated review are ratified by the full Board at its subsequent meeting.
Approval is granted with the understanding that the investigator agrees to comply with the following requirements:

1. The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.
2. The investigator is responsible for complying with all applicable guidelines and regulations regarding human research ethics conduct, as applicable to the research project.
3. Investigators must submit an annual renewal report to the REB 30 days pror to the expiration date stated on the final approval letter.
4. The investigator must not implement any deviation from, or changes to, the protocol without the approval of the REB except where necessary to eliminate an immediate hazard to the research subject, or when the change involves only logistical or administrative aspects of the study (e.g., change of telephone number or research staff). As soon as possible, however, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment(s) should be submitted to the Board for review.
5. The investigator must, prior to use, submit to the Board changes to the study documentation, e.g., changes to the informed consent letters, recruitment materials.
6. Investigators must provide the Board with French version of the consent form, unless a waiver has been granted. An interpreter should be offered to participants as required or at the request of the participant throughout the course of research.

7. For clinical drug or device trials, investigators must promptly report to the REB all adverse events that are both serious and unexpected (SAEs) or unexpected and untoward occurrences (including the loss or theft of study data and other such privacy breaches.
8. For SAE reports on clinical drug trials, the investigator must also comply with the hospital-wide Policy regarding, Procedures for Considering Medical Error in the Differential Diagnosis of Severe Adverse Events (SAE) Associated with the Drugs Administered in a Clinical Trial .
9. Investigators must promptly report to the REB any new information regarding the safety of research subjects (e.g., changes to the product monograph or investigator's brochure of drug trials). Where available, any reports produced by the Data Safety Monitoring Board should also be promptly submitted to the REB.
10. Investigators must notify the REB of any study closures (closed to accrual, temporary, premature or permanent).
11. Investigators must submit a final report at the conclusion of the study.

If you have any questions, pertaining to this letter, please contact the Research Ethics Board Office at (613) 737-7600, ext. 3350 or 2128.

REB Protocol No 17/85X - Approval of Minor Modification

CHEO Research Ethics Board
Approval - Minor Modification

Principal Investigator: Mr. Jiale Hu
REB Protocol No: 17/85X
Romeo File No: 20170268
Project Title: CHEOREB# 17/85X - Validating Skin Conductance for Assessing Pain and Stress in Mechanically Ventilated Infants
Primary Affiliation: Clinical Research\Nursing
Protocol Status: Active

Date Modifications Approved: July 12, 2018
Documents Reviewed & Approved:

Document Name	Comments	Version Date
Consent Form	Parent Information and Consent Form	2018/06/26
Other Document	Appendix A-Eligibility Checklist	2018/06/26
Protocol	Protocol	2018/06/26

The CHEO REB has reviewed and granted approval of the study documents listed above; which is to be conducted under the auspices of CHEO and/or CHEO Research Institute by the investigator noted above. The minor modification was reviewed in the delegated stream and approved by the Chair, and will be ratified by the full Board at its subsequent meeting.

Approval is granted with the understanding that the investigator agrees to comply with the following requirements:

1. The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.
2. The investigator is responsible for complying with all applicable guidelines and regulations regarding the ethical conduct of research with humans, as applicable to the research project.
3. Investigators must obtain annual renewal approval prior to the expiry date stated on the final approval letter.
4. The investigator must not implement any deviation from, or changes to, the protocol without the approval of the REB except where necessary to eliminate an immediate hazard to the research subject, or when the change involves only logistical or administrative aspects of the study (e.g., change of telephone number or research staff). As soon as possible, however, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the Board for review and approval.

5. The investigator must, prior to use, obtain approval from the Board for changes to the study documentation, e.g., changes to the informed consent letters, recruitment materials.
6. Investigators must obtain approval from the Board for French version(s) of the consent/assent form(s), unless a waiver has been granted. An interpreter should be offered to participants as required or at the request of the participant throughout the course of research.
7. For clinical drug or device trials, investigators must promptly report to the REB all adverse events that are both serious and unexpected (SAEs) or unexpected and untoward occurrences (including the loss or theft of study data and other such privacy breaches).
8. For SAE reports on clinical drug or device trials, the investigator must also comply with the hospital-wide Policy regarding, Procedures for Considering Medical Error in the Differential Diagnosis of Severe Adverse Events (SAE) Associated with the Drugs Administered in a Clinical Trial
9. Investigators must promptly report to the REB any new information regarding the safety of research participants (e.g., changes to the product monograph or investigator's brochure for drug trials). Where available, any reports produced by the Data Safety Monitoring Board should also be promptly submitted to the REB for acknowledgement.
10. Investigators must notify the REB of any study closures (closed to accrual, temporary, premature or permanent).
11. Investigators must submit a study closure event form at the conclusion of the study.

The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.

The CHEO REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonization Good Clinical Practice Consolidated Guideline (ICH GCP) ; Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; And Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The CHEO REB is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).
If you have any questions, pertaining to this letter, please contact the Research Ethics Board office at (613) 737-7600, ext. 3350 or 2128.
Regards,

Richard Carpentier, PhD
Chair, Research Ethics Board
Président, Comité d'éthique de la recherche

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

LETTRE D'APPROBATION ADMINISTRATIVE | LETTER OF ADMINISTRATIVE APPROVAL

Numéro de dossier / Ethics File Number	A08-17-06
Titre du projet / Project Title	Validating Skin Conductance for Assessing Pain and Stress in Mechanically Ventilated Infants
Type de projet / Project Type	Thèse de doctorat / PhD thesis
CÉR primaire / Primary REB	CHEO REB
Statut du projet / Project Status	Approbation administrative / Administrative Approval
Date d'approbation (jj/mm/aaaa) / **Approval Date** (dd/mm/yyyy)	31/08/2017
Date d'expiration (jj/mm/aaaa) / **Expiry Date** (dd/mm/yyyy)	15/05/2018

Équipe de recherche / Research Team

Chercheur / Researcher	*Affiliation*	*Role*
Denise Harrison	École des sciences infirmières / School of Nursing	Supervisor
Jiale Hu	École des sciences infirmières / School of Nursing	Student-researcher

Conditions spéciales ou commentaires / Special conditions or comments:

L'Université d'Ottawa a signé une Entente, conforme aux exigences de la plus récente version de l'EPTC et tout autre règlement ou législation applicable, permettant au CÉR ci-haut nommé d'être désigné comme CÉR primaire pour les projets de recherche où

1) les activités principales de recherche sont menées sous l'autorité ou sous les auspices de l'établissement lié au CÉR primaire et
2) Une partie du projet est également réalisé sous l'autorité ou sous les auspices de l'Université d'Ottawa.

Cette lettre confirme que l'Université d'Ottawa a autorisé que le CÉR primaire soit le CÉR officiel pour l'évaluation et la supervision de ce projet de recherche. Ceci n'est pas une approbation éthique.

Afin de nous aider à garder votre dossier à jour, veuillez soumettre une copie de toutes demandes de modification, renouvellement d'approbation éthique etc. soumis à et approuvé par le CÉR primaire dès qu'elles sont disponibles.

Cette approbation administrative est valide pour la durée indiquée ci-haut et est sujette aux conditions énumérées dans la section intitulée « Conditions spéciales ou commentaires ».

The University of Ottawa has signed an Agreement, compliant with current TCPS guidelines and any other applicable guidelines or legislation regarding multisite review, allowing the REB named above to serve as Board of Record (BoR) for research projects where

1) the main research activities are conducted within the auspices or jurisdiction of the BoR's institution and
2) parts of the project are also conducted under the jurisdiction or auspices of the University of Ottawa.

This letter confirms that the University of Ottawa has authorized the REB named above to serve as Board of Record for the review and oversight of this research project. This is not an REB approval.

In order to help us keep your file up to date, please submit a copy of all amendment requests, project renewals or any other changes submitted to and approved by the BoR, as they become available.

Administrative approval is valid for the period indicated above and is subject to the conditions listed in the section entitled "Special conditions or comments".

Catherine Paquet
Directrice/Director

550, rue Cumberland, pièce 154 550 Cumberland Street, Room 154
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada
613-562-5387 • 613-562-5338 • ethique@uOttawa.ca / ethics@uOttawa.ca
http://www.recherche.uottawa.ca/deontologie | http://www.research.uottawa.ca/ethics

uOttawa

Renewal of ethics certificate - A08-17-06

1 message

Dear Researchers,

Thank you for submitting the annual status report for your research project entitled: "**Validating Skin Conductance for Assessing Pain and Stress in Mechanically Ventilated Infants**" (file #: A08-17-06)

Your ethical approval certificate is renewed and **valid until May 15th, 2019** (same as CHEO REB). In order to help us keep your file up to date, please forward us a copy of any and all renewal, amendment and/or closure reports submitted to and approved by the CHEO REB, as they become available.

A reminder that if you have received a grant for your research, you must provide a copy of your renewed ethics certificate to Research Management Services.

Please don't hesitate to contact us if you have questions.

Best regards,

Marc Alain Bonenfant

Coordonnateur à l'éthique de la recherche / Research Ethics Coordinator

Bureau d'éthique et d'intégrité de la recherche / Office of Research Ethics and Integrity
Université d'Ottawa / University of Ottawa
Tél : 613-562-5387

Fax : 613-562-5338
550 Cumberland (Pavillon Tabaret Hall), salle/Room 154
Ottawa, ON K1N 6N5

http://recherche.uottawa.ca/deontologie/

Appendix B. Research Funding Letters

550 West North Street
Indianapolis, Indiana 46202
stti@stti.iupui.edu
www.nursingsociety.org

Phone 317.634.8171
Fax 317.634.8188
U.S./Canada 888.634.7575
International +800.634.7575.1

Wednesday, 21 February 2018

Congratulations, Jiale Hu, PhD(C):

On behalf of Sigma, I am pleased to inform you that your proposal, "Validating Skin Conductance for Assessing Pain and Stress in Mechanically Ventilated Infants", has been selected to receive the 2017 Sigma Theta Tau International/Rosemary Berkel Crisp Research Award in the amount of $5000. As a reminder, studies submitted without an IRB/ERB approval have two months past the funding date to forward a copy of the official IRB/ERB approval to me, via email. Studies that do not have the approval by the designated timeline will not be funded and will be forfeited.

Your grant funding period begins on Friday, 1 June 2018 and ends on Friday, 31 May 2019. Please note that funding is not retroactive. Expenditures made before Friday, 1 June 2018 will not be covered by this grant. Final reports are due to honor society headquarters 90 days after the end of the funding period. The funding period ends Friday, 31 May 2019. Once your final report is received, the remaining $500 of your grant will be sent. Guidelines for completing the final report can be found on the society's Web site at:

http://www.nursingsociety.org/advance-elevate/research/research-grants/guidelines-for-preparing-the-grant-final-report-for-the-honor-society-of-nursing-sigma-theta-tau-international

Along with sending your final report, we would like for you to include a short testimonial on how receiving the grant has helped you with your research. This information can be in the form of an email, or as a word attachment and sent to tonna@stti.org.

Grant recipients must submit a full report (i.e., grey literature: the working paper, progress report, etc.) of their investigation/research results to the Virginia Henderson Global Nursing e-Repository. Grant recipients retain full copyright to all works submitted to the repository and may choose to distill/refine the information contained in the working paper and submit an article/book manuscript to the journal/publisher of their choice for tenure and/or promotion purposes. Most publishers do not consider the public dissemination of grey literature to be "prior publishing." If the grant recipient is working with a publisher and has concerns about submitting the full report to the repository, an embargo period may be requested to avoid perceived interference with the journal/book publication process. Embargo periods will be considered on a case-by-case basis and will not extend beyond industry standards. The repository will display general item information during the embargo period, but the full-text attached file will not be accessible to the public for a set period of time. To submit a full report or for additional information, visit www.nursingrepository.org and select the "Get Started" tab. If you have additional questions, contact Kimberly Thompson, repository manager, by phone at 888.634.7575 (U.S./Canada toll-free) or via email at repository@stti.org.

In order to process your grant funds, you **must** complete the grant acceptance information found by linking to the following site:

http://stti.grant.confex.com/stti_grant/december1718/speakerscorner.cgi

If you are awarded additional funding for the same budget items covered in your Sigma Theta Tau International/Rosemary Berkel Crisp Research Award, contact Tonna Thomas at the honor society (research@stti.iupui.edu). All funding agencies to which you have submitted your proposal need to be notified of the receipt of this grant.

The reviewers' comments about your proposal are available by going to:

http://stti.grant.confex.com/stti_grant/december1718/app/papers/reviewercomments.cgi?recordid=13736&password=448893

We wish you success in your study and look forward to the contribution your work will make to the discipline of nursing and to health care.

If your grant funding check will be issued to you as an individual and you in North America, please contact Tonna M. Thomas at tonna@stti.iupui.edu to request a W9 form. Checks will **not** be issued without this

information. Please check with your tax advisor for clarification regarding research grants and personal gross income.

Kind Regards,

Tonna M. Thomas, MS
Sigma, Grants Coordinator
Sigma Foundation for Nursing
550 W. North Street
Indianapolis, IN 46202 USA
888.634.7575 (US/Canada)
Direct line: +1.317.917.4954
Fax: +1.317.634.8188
Email: tonna@stti.org

the CANADIAN PAIN SOCIETY
la SOCIÉTÉ CANADIENNE de la DOULEUR
250 Consumers Road, Suite 301 • Toronto, ON • M2J 4V6 • T: 416-642-6379 • office@canadianpainsociety.ca • www.canadianpainsociety.ca

April 2018

Dear Jiale Hu

Congratulations! You are the recipient of the Canadian Pain Society (CPS) **2018 Trainee Research Award** (Clinical Science).

As a recipient of this award, the $2,000 grant will be distributed to your institution directly from the CPS. In response to this email, please provide us with complete payment details, including to whom the grant should be made payable, along with the address and any other particulars (i.e., banking details) that we will need to complete the money transfer.

While you are not obligated to attend the 39th Annual Scientific Meeting, if you do attend you will receive a complimentary ticket to the 2018 Awards Gala on May 24, 2018 in Montreal, Quebec, where the award will be announced. Please contact the office to confirm your attendance and to receive your complimentary Awards Gala ticket.

Again, congratulations on a successful application.

Warm regards,

Laura Stone, PhD
Chair, Awards Committee
Canadian Pain Society

cc: B. Cairns, President, CPS

Appendix C. Recruitment Posters for Parents

RESEARCH INSTITUTE
INSTITUT DE RECHERCHE

uOttawa

Validating Skin Conductance for Assessing Pain and Stress in Mechanically Ventilated Infants

What is the study about?
Over the past several years we have learned about how babies react when they have something painful done to them, like pricking their heel for a blood test or having a tube inserted. In the hospital, it is important for health care providers to regularly check to see if babies are in pain, but we are still learning about the best ways to do this. In this study, we want to learn about using a device (called a skin conductance monitor) to see how much pain and stress a baby is experiencing during different procedures. The babies in this study will all be patients in the Neonatal Intensive Care Unit (NICU) at the Children's Hospital of Eastern Ontario (CHEO) who are mechanically ventilated.

Who can participate?
We are asking your baby to be in this study because he/ she is less than one year old, and is having a blood test done in NICU at CHEO.

What is involved in participating?
If you agree to participate in this study, we will put three tiny sticky pads (called "electrodes") on your baby's hand or foot. These pads are not harmful and will not cause any pain to your baby. We will videotape your baby before, during and three minutes after completion of two procedures that your baby is receiving as part of their routine care: (1) a required painful procedure such as a blood test or gastric tube insertion; and (2) a required non-painful procedure such as a diaper change. The information from the skin conductance monitor and the videos will be used to see how much pain and distress your baby was showing during the procedures.

Where will the study take place?
The study will take place in NICU at CHEO.

Contact information:
If you are interested in participating in this research study, please contact:

Jiale Hu
Principal Investigator
Research Institute
Children's Hospital of Eastern Ontario
401 Smyth Road
Ottawa, Ontario
K1H 8L1
Phone: 613-737-7600 ext 6027
Email: jhu@cheo.on.ca

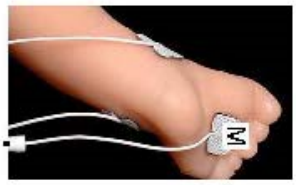
This study has been approved by the CHEO Research Ethics Board.

Protocol Number: 17/85X

Version date: August 17th, 2017 Page **1** of **1**

Appendix D. Recruitment Posters for Staff

Validating Skin Conductance (SC) for Assessing Pain and Stress in Mechanically Ventilated Infants



Principal Investigator:
Jiale (Gary) Hu, RN, PhD(C)
CHEO Research Institute
University of Ottawa
jhu@cheo.on.ca
613-737-7600 ext 6027

Supervisors:
Denise Harrison, RN, PhD
Chair in Nursing Care of Children, Youth and Families, CHEO
dharrison@cheo.on.ca
613-737-7600 ext 4140

JoAnn Harrold
Medical Director
NICU, CHEO
jharrold@cheo.on.ca
613-737-7600 ext 2417

Purpose

We are evaluating SC as a measure of pain and stress during painful and non-painful procedures that the mechanically ventilated infants need as part of their care. The total sample size is expected to be **55** mechanically ventilated infants from OCT 2017 to DEC 2018.

How will the study affect you?

We will be asking bedside nurses to check if parents are interested in talking with us about the study. We will conduct the informed consent discussion. After the consent is obtained, We will discuss with bedside nurses about the time of doing painful and non-painful procedures. Video recording and SC monitoring of the patients will be performed by us during each type of the procedure only once.

YOU CAN HELP US!

If parents of eligible patients are available or enrolled patients have scheduled painful or non-painful procedures,

Please contact Gary through **Phone #613-255-3981!**

This study has been approved by the CHEO and Uottawa REBs

uOttawa CHEO CHEO RESEARCH INSTITUTE INSTITUT DE RECHERCHE

Appendix E. Eligibility Criteria Checklist for Consent

Eligibility Criteria Checklist for Consent

Subject Initials: _____

Inclusion Criteria ***Must answer YES to be enrolled***	**YES**	**NO**
Infant is up to 12 months.		
Infant is an inpatient of NICU at CHEO.		
Infant is mechanically ventilated.		
Infant is requiring a painful procedure, such as heel lance or other skin-breaking procedures, and non-painful care, such as diaper change or positioning.		
Parents/guardians are able to understand English or French.		
Exclusion Criteria ***Must answer NO to be enrolled***	**YES**	**NO**
Infant is less than a corrected age of 25 weeks.		
Infant has any injury to the skin where the SC probes need to be placed.		
Infant has an implanted defibrillator or pacemaker.		
Infant has spinal cord malformation (e.g. myelomeningocele and sacral teratoma).		
Infant has high dose of cholinergic active / blocking drugs (e.g. neostigmine, glycopyrrolate, and atropine) in past 8 hours.		

Name of Person Checking the Eligible Criteria (printed): _____

Signature of Person Checking the Eligible Criteria: _____

Date: _____

Appendix F. Eligibility Criteria Checklist for Consent (Minor modification)

Eligibility Criteria Checklist for Consent

Subject Initials: _____

Inclusion Criteria ***Must answer YES to be enrolled***	**YES**	**NO**
Infant is up to 12 months.		
Infant is an inpatient of NICU or PICU at CHEO.		
Infant is mechanically ventilated.		
Infant is requiring a painful procedure, such as heel lance or other skin-breaking procedures, and non-painful care, such as diaper change or positioning.		
Parents/guardians are able to understand English or French.		
Exclusion Criteria ***Must answer NO to be enrolled***	**YES**	**NO**
Infant is less than a corrected age of 25 weeks.		
Infant has any injury to the skin where the SC probes need to be placed.		
Infant has an implanted defibrillator or pacemaker.		
Infant has spinal cord malformation (e.g. myelomeningocele and sacral teratoma).		
Infant has high dose of cholinergic active / blocking drugs (e.g. neostigmine, glycopyrrolate, and atropine) in past 8 hours.		

Name of Person Checking the Eligible Criteria (printed): _____

Signature of Person Checking the Eligible Criteria: _____

Date: _____

Appendix G. Parent Information and Consent Form

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

Parent Information and Consent Form

Validating Skin Conductance for Assessing Pain and Stress in Mechanically Ventilated Infants

---

Principal Investigator: Jiale Hu
PhD Candidate
School of Nursing
University of Ottawa
451 Smyth Rd
Research Assistant
Research Institute
Children's Hospital of Eastern Ontario
401 Smyth Road
Ottawa, Ontario, K1H 8L1
Phone: 613-737-7600 ext 6027
Email: jhu@cheo.on.ca

Co-investigators:

Denise Harrison
Chair in Nursing Care of Children, Youth and Families
Children's Hospital of Eastern Ontario
401 Smyth Road
Ottawa, Ontario, K1H 8L1
Phone: 613-737-7600 ext 4140
Email: dharrison@cheo.on.ca

JoAnn Harrold
Medical Director
NICU, CHEO
Children's Hospital of Eastern Ontario
401 Smyth Road
Ottawa, Ontario, K1H 8L1
Phone: 613-737-7600 ext 2417
Email: jharrold@cheo.on.ca

You are being invited to join a research study that is looking at the use of a device to monitor a mechanically ventilated infant's pain and stress during different procedures. You are being invited to join this study because your baby is admitted to the Neonatal Intensive Care Unit (NICU) at the Children's Hospital of Eastern Ontario (CHEO). Before agreeing to take part in this study, it is important that you read and understand this document.

Taking part in this study is voluntary. Your decision to participate or not in this study will not affect the care you receive at CHEO. You are free to withdraw your baby from the study at any time and there will be no penalty to you or your baby. You may do so by contacting the Principal Investigator or Co-Investigator. Your decision to participate or not in the study will not influence the care you receive at CHEO. When your baby is withdrawn from the study, you choose to allow the research team to have their infants' data already collected in the study kept for analysis or have the PI destroy all the data. Reasons for withdrawal will be recorded in the screening log and master list.

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

Why is this study being done?

Over the past several years we have learned a lot about pain in babies, but we still have more to learn about improving pain measurement for babies, especially for babies who are sick and hospitalized. The purpose of this study is to evaluate the use of skin conductance (SC) for assessing pain and stress in mechanically ventilated babies who are admitted to the NICU at CHEO. In this study, we are hoping to find out if SC is an accurate way to measure pain during procedures that your baby needs as part of their care. There will be no extra painful procedures as a result of the study and the use of the SC monitor is not invasive. There is no change in the normal care given to your baby during procedures and you will be encouraged to comfort your baby in your normal way.

Why is your baby being asked to be in this research project?

We are asking your baby because he/ she is less than one year old, and having a blood test or gastric tube insertion done in the NICU at CHEO

How many people will participate?

At CHEO, we expect to have 55 ventilated babies participate in this study. The study is expected to be recruiting for 12 months.

What will I have to do?

If you agree to participate in this study, we will observe your baby during two required procedures:

- One required painful procedure, such as blood sampling;
- One required non-painful procedure, such as diaper change

During these two observations, we will:

- Attach SC monitoring electrodes (similar to bedside monitor electrodes) to your baby's hand or foot 10 minutes before the start of the procedure until 3 minutes after the end of the procedure; and
- Videotape your baby 3 minutes before the start of the procedure until 3 minutes after the end of the procedure

These SC data and videos will be used to score pain and distress.

Are there any risks to participating?

This is a low risk study as it just involves extra monitoring for a short period of time. Risk of the skin conductance monitor is no different to bedside monitoring. It is therefore highly unlikely that there will any adverse events related to SC monitoring. There were no side effects of SC monitoring in our previous studies using SC monitoring. We do not expect any risks, side effects or discomforts associated with using SC monitoring as part of this project. The Investigator may stop your participation in the research study without regard to your consent if there are any concerns regarding safety or risk.

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

Are there any benefits to participating?

As an observational study, there is no immediate benefit to the participants of this study. However, the findings of study might help us to learn about the accuracy of the SC device that may be used in the future for critically ill babies to monitor pain continuously and support health care providers to provide better pain treatment.

Will I be paid to participate?

You will not be paid to take part in this study.

What if I get injured?

In the event that your baby suffers injury as a direct result of participating in this study, normal legal rules on compensation will apply. Medical care will be provided to you or your child. By signing this consent form you are in no way waiving your legal rights or releasing the investigator from their legal and professional responsibilities.

Will I be told about new information?

We will inform you of any new information that might influence your decision to continue to participate in this research project. We will ask you again if you still want to be in the study. You will be offered a summary of the study results which can be mailed to you by post, or emailed to you. This summary will include all babies, so will not be about your baby specifically, as no individual baby will be identifiable.

What about confidentiality and privacy?

For this study we will be collecting your baby's sex, age, weight at birth, diagnosis, details about surgeries, and current medications for the research purposes described in this consent form. Representatives from the CHEO Research Ethics Board and CHEO quality improvement reviewers may look at your records at the site where these records are held, to check that the study is following the proper laws and guidelines. Your personal information will be kept strictly confidential except as required or permitted by law. Any information that would indicate that a child was being harmed or at risk of such harm, would not be kept confidential and instead be disclosed as appropriate to the appropriate authorities.

Participants will be assigned and thereafter, be identified by a unique identification study number and all data collection forms will be identified by the study code number. The data (including all completed files, video footage, and forms) produced from this study will be stored in a locked file in the investigator's office. Study computer files, including the video recordings, and databases will be password protected and accessible only in the computer residing in the locked office used by the investigators. No identifying information will be presented or published. Following completion of the research study the data will be kept for 7 years after the last publication of this study. They will then be destroyed.

You or your baby will not be identified in any publication or presentation of this study.

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

We may want to use the video recordings in public presentations related to the research. There is a Media Records Release Form attached that outlines several possible uses and asks for your specific consent to use these items in each way. If you agree to allow these items to be used after this research study is over, please read, initial, and sign the Media Records Release Form in addition to this consent form. We will not use any video recordings, or other identifiable information about you in any future presentation without your consent.

Is the research team benefiting from the study?

The research team members are not benefiting personally, financially or in some other way from this study.

What if I have questions?

If you have any questions concerning your baby's participation in the study, or if at any time you feel that your baby has experienced a study-related injury, or if you would like more information, please contact the Principal Investigator, Jiale Hu at 613-737-7600 ext 6027.

The CHEO Research Ethics Board (REB) has reviewed and approved this research project. The REB is a committee of the hospital that includes individuals from different professional backgrounds. The Board reviews all research that takes place at the hospital. Its goal is to ensure the protection of the rights and welfare of people participating in research. The Board's work is not intended to replace a parent or baby's judgment about what decisions and choices are best for them. You may contact the Chair of the Research Ethics Board, for information regarding patient's rights in research studies at 613-737-7600 x 3272, although this person cannot provide any health-related information about the study.

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

Consent Form Signatures

To become a part of this study, you must sign this page.

By signing this consent form I agree that:

- I am voluntarily agreeing to participate in this research study;
- I understand the information within this consent form;
- All of the risks and benefits of participation have been explained to me;
- All of my questions have been answered;
- I allow access to my medical records and/or personal information as described in this consent form; and
- I do not give up my legal rights by signing this form.

A copy of the signed Information Sheet and/or Consent Form will be provided to me.

_____
Name of baby

_____ _____
Name of person giving consent Relationship to infant

_____ _____
Signature of person giving consent Date

_____ _____ _____
Name of person obtaining consent Signature Date

Study Results

I wish to receive a summary of the findings once this study has been completed: Yes ☐ No ☐

Please provide your email or mailing address and we will send you a copy of the study results:

Parent email or mailing address:

_____

_____

Appendix H. Parent Information and Consent Form (Minor Modification)

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

Parent Information and Consent Form

Validating Skin Conductance for Assessing Pain and Stress in Mechanically Ventilated Infants

---

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Medical Director
NICU, CHEO
Children's Hospital of Eastern Ontario
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Ottawa, Ontario, K1H 8L1
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You are being invited to join a research study that is looking at the use of a device to monitor a mechanically ventilated infant's pain and stress during different procedures. You are being invited to join this study because your baby is admitted to the Neonatal Intensive Care Unit (NICU) or Pediatric Intensive Care Unit (PICU) at the Children's Hospital of Eastern Ontario (CHEO). Before agreeing to take part in this study, it is important that you read and understand this document.

Taking part in this study is voluntary. Your decision to participate or not in this study will not affect the care you receive at CHEO. You are free to withdraw your baby from the study at any time and there will be no penalty to you or your baby. You may do so by contacting the Principal Investigator or Co-Investigator. Your decision to participate or not in the study will not influence the care you receive at CHEO. When your baby is withdrawn from the study, you choose to allow the research team to have their infants' data already collected in

the study kept for analysis or have the PI destroy all the data. Reasons for withdrawal will be recorded in the screening log and master list.

Why is this study being done?

Over the past several years we have learned a lot about pain in babies, but we still have more to learn about improving pain measurement for babies, especially for babies who are sick and hospitalized. The purpose of this study is to evaluate the use of skin conductance (SC) for assessing pain and stress in mechanically ventilated babies who are admitted to the NICU or PICU at CHEO. In this study, we are hoping to find out if SC is an accurate way to measure pain during procedures that your baby needs as part of their care. There will be no extra painful procedures as a result of the study and the use of the SC monitor is not invasive. There is no change in the normal care given to your baby during procedures and you will be encouraged to comfort your baby in your normal way.

Why is your baby being asked to be in this research project?

We are asking your baby because he/ she is less than one year old, and having a blood test or gastric tube insertion done in the NICU or PICU at CHEO

How many people will participate?

At CHEO, we expect to have 55 ventilated babies participate in this study. The study is expected to be recruiting for 12 months.

What will I have to do?

If you agree to participate in this study, we will observe your baby during two required procedures:

- One required painful procedure, such as blood sampling;
- One required non-painful procedure, such as diaper change

During these two observations, we will:

- Attach SC monitoring electrodes (similar to bedside monitor electrodes) to your baby's hand or foot 10 minutes before the start of the procedure until 3 minutes after the end of the procedure; and
- Videotape your baby 3 minutes before the start of the procedure until 3 minutes after the end of the procedure

These SC data and videos will be used to score pain and distress.

Are there any risks to participating?

This is a low risk study as it just involves extra monitoring for a short period of time. Risk of the skin conductance monitor is no different to bedside monitoring. It is therefore highly unlikely that there will any adverse events related to SC monitoring. There were no side effects of SC monitoring in our previous studies using SC monitoring. We do not expect any risks, side effects or discomforts associated with using SC

monitoring as part of this project. The Investigator may stop your participation in the research study without regard to your consent if there are any concerns regarding safety or risk.

Are there any benefits to participating?

As an observational study, there is no immediate benefit to the participants of this study. However, the findings of study might help us to learn about the accuracy of the SC device that may be used in the future for critically ill babies to monitor pain continuously and support health care providers to provide better pain treatment.

Will I be paid to participate?

You will not be paid to take part in this study.

What if I get injured?

In the event that your baby suffers injury as a direct result of participating in this study, normal legal rules on compensation will apply. Medical care will be provided to you or your child. By signing this consent form you are in no way waiving your legal rights or releasing the investigator from their legal and professional responsibilities.

Will I be told about new information?

We will inform you of any new information that might influence your decision to continue to participate in this research project. We will ask you again if you still want to be in the study. You will be offered a summary of the study results which can be mailed to you by post, or emailed to you. This summary will include all babies, so will not be about your baby specifically, as no individual baby will be identifiable.

What about confidentiality and privacy?

For this study we will be collecting your baby's sex, age, weight at birth, diagnosis, details about surgeries, and current medications for the research purposes described in this consent form. Representatives from the CHEO Research Ethics Board and CHEO quality improvement reviewers may look at your records at the site where these records are held, to check that the study is following the proper laws and guidelines. Your personal information will be kept strictly confidential except as required or permitted by law. Any information that would indicate that a child was being harmed or at risk of such harm, would not be kept confidential and instead be disclosed as appropriate to the appropriate authorities.

Participants will be assigned and thereafter, be identified by a unique identification study number and all data collection forms will be identified by the study code number. The data (including all completed files, video footage, and forms) produced from this study will be stored in a locked file in the investigator's office. Study computer files, including the video recordings, and databases will be password protected and accessible only in the computer residing in the locked office used by the investigators. No identifying information will be

presented or published. Following completion of the research study the data will be kept for 7 years after the last publication of this study. They will then be destroyed.

You or your baby will not be identified in any publication or presentation of this study.

We may want to use the video recordings in public presentations related to the research. There is a Media Records Release Form attached that outlines several possible uses and asks for your specific consent to use these items in each way. If you agree to allow these items to be used after this research study is over, please read, initial, and sign the Media Records Release Form in addition to this consent form. We will not use any video recordings, or other identifiable information about you in any future presentation without your consent.

Is the research team benefiting from the study?

The research team members are not benefiting personally, financially or in some other way from this study.

What if I have questions?

If you have any questions concerning your baby's participation in the study, or if at any time you feel that your baby has experienced a study-related injury, or if you would like more information, please contact the Principal Investigator, Jiale Hu at 613-737-7600 ext 6027.

The CHEO Research Ethics Board (REB) has reviewed and approved this research project. The REB is a committee of the hospital that includes individuals from different professional backgrounds. The Board reviews all research that takes place at the hospital. Its goal is to ensure the protection of the rights and welfare of people participating in research. The Board's work is not intended to replace a parent or baby's judgment about what decisions and choices are best for them. You may contact the Chair of the Research Ethics Board, for information regarding patient's rights in research studies at 613-737-7600 x 3272, although this person cannot provide any health-related information about the study.

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

Consent Form Signatures

To become a part of this study, you must sign this page.

By signing this consent form I agree that:

- I am voluntarily agreeing to participate in this research study;
- I understand the information within this consent form;
- All of the risks and benefits of participation have been explained to me;
- All of my questions have been answered;
- I allow access to my medical records and/or personal information as described in this consent form; and
- I do not give up my legal rights by signing this form.

A copy of the signed Information Sheet and/or Consent Form will be provided to me.

_____
Name of baby

_____ _____
Name of person giving consent Relationship to infant

_____ _____
Signature of person giving consent Date

_____ _____ _____
Name of person obtaining consent Signature Date

Study Results

I wish to receive a summary of the findings once this study has been completed: Yes ☐ No ☐

Please provide your email or mailing address and we will send you a copy of the study results:

Parent email or mailing address:

_____

Appendix I. Research Media Records Release Form

Research Media Records Release Form

MEDIA CONSENT FORM

(Plaque)

I, _____ hereby grant permission to the Children's Hospital of
(Parent/Guardian/Patient)

Eastern Ontario (CHEO) and any other person authorized by the hospital to take and produce photographs, film, sound recordings and any other audio and/or visual reproductions of myself or my child. Formats may include, but are not limited to: television, radio, print and internet (web).

I consent to these photographs or video recordings being used for:

- ☐ This study only: Validating Skin Conductance for Assessing Pain and Stress in Mechanically Ventilated Infants
- ☐ Education/ training purposes (i.e. conferences, presentations)
- ☐ Promotion for public related events (i.e. pediatric pain public awareness)
- ☐ CHEO related public fundraising events

Participant Name:_____

Participant Date of Birth:_____

Name of Parent/Guardian (print):_____

Parent/Guardian Signature :_____Date :_____

Hospital Representative:_____Date :_____

NOTES:

_____

_____

_____

_____

Protocol Number: 17 85X

Version date: August 17th, 2017

Appendix J. Data Collection Form I

Data Collection Form I

Demographic Characteristics and Medical Information

Study subject ID: _____

Number of hospitalized days: _____**days**

Sex: □ **Female** □ **Male** **Current Weight:** _____**grams**

Gestational age at birth: _____**weeks**_____**days** **Postnatal age:** _____**weeks**_____**days**

Major Clinical Diagnosis: _____

_____

_____

Number of previous surgery:_____ **Number of days after most recent surgery:**_____

Type of most recent surgery: _____

_____

_____

Neonatal Therapeutic Intervention Scoring System:____**Number of days on ventilation:**___

Ventilation status: _____

Observation for (maybe multiple answers): ◇**Painful procedure** ◇**Non-painful procedure**

Any medication for 24 hours prior to observation which might affect patient pain intensity

Medication	Time prior to observation	Infusion vs Bolus	Dose
	_____**hours**_____**minutes**	□**Infusion** □**Bolus**	
	_____**hours**_____**minutes**	□**Infusion** □**Bolus**	

	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	
	_____hours_____minutes	**□Infusion □Bolus**	

Additional Comments:

_____

_____

_____

***Data collection form Instruction:**

Commonly used medication in NICU which might affect patient pain intensity

Opioids:

- Morphine
- Fentanyl

Muscle Relaxants:

- Succinylcholine
- Vecuronium
- Pancuronium

Sedatives:

- Chloral Hydrate
- Midazolam (Versed)
- Benzodiazepines:
    - Lorazepam (Ativan)
    - Diazepam (Valium)

Anticonvulsants:

- Phenobarbital
- Dilantin

Appendix K. Neonatal Therapeutic Intervention Scoring System (NTISS)

Item	Subscore
Respiratory	
Supplemental oxygen	1[a]
Surfactant administration	1
Tracheostomy care	1[b]
Continuous positive airway pressure administration	2 [a]
Endotracheal intubation	2
Mechanical ventilation	3 [a]
Mechanical ventilation with muscle relaxant	4 [a]
High-frequency ventilation	4 [a]
Extracorporeal membrane oxygenation	4
Cardiovascular	
Indomethacin administration	1
Volume expansion (≤15ml/kg)	1
Vasopressor administration (1 agent)	2[d]
Volume expansion (>15ml/kg)	3[c]
Vasopressor administration >1 agent	3 [d]
Pacemaker on standby	3[e]
Pacemaker used	4 [e]
Cardiopulmonary resuscitation	4
Drug therapy	
Antibiotic administration (≤ 2 agents)	1[f]
Diuretic administration (enteral)	1[g]
Steroid administration (postnatal)	1
Anticonvulsant administration	1
Aminophylline administration	1
Other unscheduled medication	1
Antibiotic administration (>2 agents)	2[f]
Diuretic administration (parenteral)	2[g]
Treatment of metabolic acidosis	3
Potassium binding resin administration	3
Monitoring	
Frequent vital signs	1
Cardiorespiratory monitoring	1
Phlebotomy (5-10 blood draws)	1[h]
Thermoregulated environment	1
Noninvasive oxygen monitoring	1
Arterial pressure monitoring	1
Central venous pressure monitoring	1
Urinary catheter	1
Quantitative intake and output	1

Extensive phlebotomy (>10 blood draws)	2[h]
Metabolic/nutrition	
Gavage feeding	1
Intravenous fat emulsion	1
Intravenous amino acid solution	1
Phototherapy	1
Insulin administration	2
Potassium Infusion	3
Transfusion	
Intravenous gamma globulin	1
Red blood cell transfusion (≤15ml/kg)	2[i]
Partial volume exchange transfusion	2
Red blood cell transfusion (>15ml/kg)	3[f]
Platelet transfusion	3
White blood cell transfusion	3
Double volume exchange transfusion	3
Procedural	
Transport of patient	2
Single chest tube in place	2[j]
Minor operation	2[k]
Multiple chest tubes in place	3[j]
Thoracentesis	3
Major operation	4[k]
Pericardiocentesis	4[l]
Pericardial tube in place	4[l]
Dialysis	4
Vascular access	
Peripheral intravenous line	1
Arterial line	2
Central venous line	2

* Superscript letters represent mutually exclusive variables

Appendix L. Data Collection Form II

Data Collection Form II

Study subject ID: _____

Observation for: □ **Painful procedure** □ **Non-painful procedure**

1. Baseline Information

Baseline Behavioural State:_____

(0: Active and Awake, 1: Quiet and Awake, 2: Active and Asleep, 3: Quiet and Asleep)

Baseline Highest HR: _____ Baseline Lowest SpO2:_____

Infant's Placement: Place _____ Position _____

2. Vital Signs Recording

Before Procedure phase

	1	2	3	4	5	6
Highest HR						
Lowest SpO2						

During procedure phase

	1	2	3	4	5	6
Highest HR						
Lowest SpO2						

After procedure phase

	1	2	3	4	5	6
Highest HR						
Lowest SpO2						

3. Procedure Information

Procedure:_____Number of Attempts: _____

Site of poking (if application): Attempt #1: Site_____

Attempt #2: Site_____; Attempt #3: Site _____

4. Medication change, patient care or unexpected painful procedures

Medication/Patient Care/ Unexpected painful procedures	Timing after observation on stop watch	Infusion/Bolus/Provider	Dose/Description
	_____min_____seconds		
	_____min_____seconds		
	_____min_____seconds		

Additional Comments:

_____

_____

Version Number: 17/85X
Version date: August 23, 2017

Appendix M. The Premature Infant Pain Profile (PIPP) - Revised (PIPP-R)

Infant Indicator	Indicator Score				Infant Indicator Score
	0	+1	+2	+3	
Change in Heart Rate (bpm) Baseline: _____	0 - 4	5 - 14	15 - 24	>24	
Decrease in Oxygen Saturation (%) Baseline: _____	0 - 2	3 - 5	6 – 8	>8 or Increase in O_2	
Brow Bulge (Sec)	None (<3)	Minimal (3 -10)	Moderate (11 – 20)	Maximal (>20)	
Eye Squeeze (Sec)	None (<3)	Minimal (3 -10)	Moderate (11 – 20)	Maximal (>20)	
Naso-Labial Furrow (Sec)	None (<3)	Minimal (3 -10)	Moderate (11 – 20)	Maximal (>20)	
				* Sub-total Score:	
Gestational Age (Wks + Days)	>36 wks	32 wks - 35 wks, 6d	28 wks- 31wks, 6d	<28wks	
Baseline Behavioural State	Active and Awake	Quiet and Awake	Active and Asleep	Quiet and Asleep	
				** Total Score:	

* Sub-total for physiological and facial indicators. If Sub-total score>0, add GA and BS indicator scores.
** Total Score: Sub-total Score + GA Score + BS Score

Scoring instructions

Step 1: Observe infant for **15 seconds at rest** and assess vital sign indicators [highest heart rate (HR) and lowest O_2 Saturation (O_2 SAT)] and behavioural state.

Step 2: Observe infant for **30 seconds after procedure** and assess **change** in vital sign indicators (maximal HR, lowest O_2 SAT and duration of facial actions observed).
* If infant requires an increase in oxygen at any point before or during procedure, they receive a score of 3 for the O_2 SAT indicator

Step 3: Score for corrected gestational age (GA) and behavioural state (BS) if the sub-total score >0.

Step 4: Calculate total score by adding **Sub-total Score + BS Score.**

Note:

Gibbins, S., Stevens, B., Yamada, J., Dionne, K., Campbell-Yeo, M., Lee, G., . . . Taddio, A. (2014). Validation of the Premature Infant Pain Profile-Revised (PIPP-R). *Early Hum Dev, 90*(4), 189-193. doi: 10.1016/j.earlhumdev.2014.01.005

Appendix N. The Four-item Subset of Neonatal Facial Coding System (NFCS)

Facial Indicators	**Scoring**
Brow bulge	**□Present (1) □absent (0)**
Eye squeeze	**□Present (1) □absent (0)**
Naso-labial furrow	**□Present (1) □absent (0)**
Open lips	**□Present (1) □absent (0)**

Appendix O. Adverse Event Report Form

Adverse Event Report Form

***As per the study protocol, Any AE that occurs between the time Skin Conductance (SC) monitoring is set up and the time the data collection is completed will be recorded.*

Protocol: ***Validating Skin Conductance for Assessing Pain and Stress in Mechanically Ventilated Infants***
Site: Children's Hospital of Eastern Ontario (CHEO)
Subject ID: _____
Observation for: □ Painful procedure □ Non-painful procedure

Adverse Event Description	Serious Adverse Event	Start Date and time YYYY/MM/DD	End Date and time YYYY/MM/DD	Severity	Relationship	Outcome	PI initials and date
	□ No □Yes*	_____/____/___ ___:___	_____/____/___ ___:___	□ Mild □ Moderate □ Severe	□ Unrelated □ Possibly □ Probably □ Definitely	□ Not Recovered/Not Resolved □ Recovered/Resolved □ Recovered/Resolved With Sequelae □ Recovering/Resolving □ Fatal □ Unknown	

** "Yes" should be answered when the adverse event results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity*

***Adverse Event Report Form Instruction**

1. Definitions

1.1 Adverse Event (AE): Any untoward medical occurrence in a child enrolled into this pilot study regardless of its causal relationship to study treatment.

1.2 Serious Adverse Event (SAE): Adverse events are classified as serious or non-serious. An SAE is defined as any AE that results in death, is immediately life threatening, requires inpatient hospitalization, results in persistent or significant disability/ incapacity. Important medical events will be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR): A SUSAR is any SAE that is both suspected to be related to the study treatment and is unexpected (i.e. not consistent with applicable product information).

2. Reporting and Monitoring of AE/SAE

2.1The severity and relationship of an AE will be assessed as per the criteria below.

2.2 The severity of an Adverse Event will be assessed as follows:

2.2.1 Mild: Events that require minimal or no treatment and do not interfere with the patient's daily activities.

2.2.2 Moderate: Events that cause sufficient discomfort to interfere with daily activity and/ or require a simple dose of medication or other treatment.

2.2.3 Severe: Events that prevent usual daily activity or require complex treatment.

2.3 The relationship of the event to the intervention will be assessed as follows:

2.3.1 Unrelated: There is no association between the study observation and the reported event. AE in this category do not have a reasonable temporal relationship to exposure to SC monitoring during the procedure, or can be explained by a commonly occurring alternative etiology.

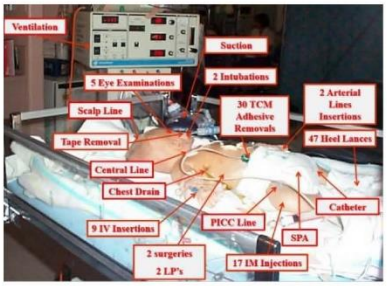
2.3.2 Possible: The event could have caused or contributed to the AE. AE in this category follow a reasonable temporal sequence from the time of SC monitoring during or following completion of the procedure, but could also have been produced by other factors.

2.3.3 Probable: The association of the event with the study intervention seems likely. AE in this category follow a reasonable temporal sequence from the time of exposure to SC monitoring and are consistent with the rare, but known possible AE of SC monitor, or judgment based on the investigator's clinical experience.

2.3.4 Definite: The AE is a consequence of administration of SC monitoring. AE in this category cannot be explained by concurrent illness, progression of disease state of concurrent medication reaction. Such events may be widely documented as having an association with SC monitoring.

Appendix P. The One-page Pamphlet for Health Care Professionals

Can skin conductance measure pain in mechanically ventilated infants?

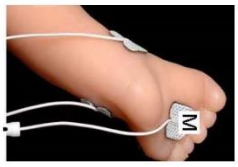


- Sick babies have up to 17 painful and distressing procedures per day in neonatal intensive care units.
- Effective treatment of pain depends on nurses and doctors being able to accurately assess babies' pain.
- Using traditional infant pain observation scales in very sick babies who need to be ventilated and who are sedated or paralyzed is challenging.

Skin conductance, a measure of sweating as results of stress, may be the answer.

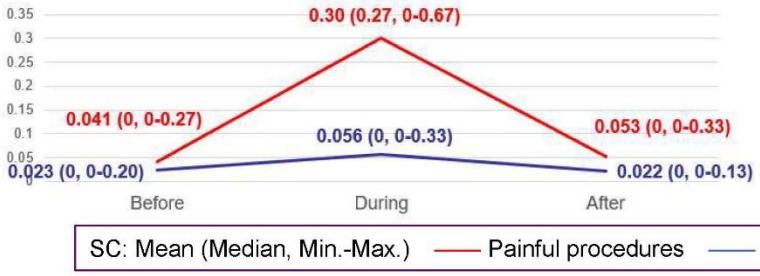
Skin Conductance (SC) measurement device

- Similar to the lie detector technology
- A measure of sweating in the hands or feet
- Sympathetic nervous system's response to stress



From October 2017 to November 2018, data for 55 infants (Median gestational age: 35 weeks 5 days, Median postnatal Age: 1 week 2 days) were collected.

- In mechanically ventilated infants, SC (number of waves per second) was
  - Significantly higher during painful procedures than non-painful procedures;
  - Significantly higher during painful procedures than baseline and recovery;
  - Not significantly higher during non-painful procedures than baseline and recovery.
  - Moderately and positively correlated with commonly used pain scales (PIPP-R and NFCS)



Yes! SC works!

SC<0.235 → 99% Infants did not have moderate-to-severe pain

SC≥0.235 → 67% Infants had moderate-to-severe pain

Thank you so much for your support and help!

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Appendix Q. The One-page Pamphlet for Parents

Can skin conductance measure pain in babies?

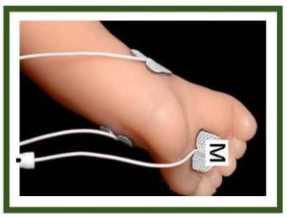
Dear Parents,

Thank you from our research team for your participation in our study about using skin conductance to measure pain in babies at CHEO.

Allowing us to study your baby during a medically necessary painful procedure as well as a non-painful procedure (such as diaper change) helped us to work out whether skin conductance was a useful and reliable measure of pain for sick babies. This is important as effective treatment of pain needs nurses and doctors to accurately assess pain. Using traditional infant pain observation scales in very sick babies who need to be ventilated and who are sedated is challenging.

Skin conductance measurement is:

- Similar to a lie detector
- A measure of sweating in the hands or feet
- A physiological response to stress



From October 2017 to November 2018, we included 55 babies from the CHEO NICU

What did we find?

- Skin conductance was higher during painful procedures compared to non-painful procedures.
- Skin conductance was higher during any procedure compare to rest.
- Skin conductance measurements were correlated with commonly used pain scales in clinical settings.

Therefore, Yes! – Skin conductance can reliably measure pain in babies

How will we use these findings?

- These findings have helped us to understand how skin conductance could measure pain in babies. We will continue to work on ways we can improve using skin conductance to help other babies in hospital the future.
- We will share the findings with nurses, doctors, researchers and other staff who look after babies. Sharing the results will help us to plan together how to use SC in the future.

We thank you again for your participation in this study!

uOttawa CHEO Ontario Sigma