Evaluating the Sphenopalatine Ganglion Block as an Alternative Treatment Method to Alleviate Pain Associated with Primary Headache Disorders in the Emergency Department

Dilan Patel

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School of Epidemiology and Public Health
Faculty of Medicine
University of Ottawa

PREFACE

Dilan Patel was primarily responsible for all aspects of this thesis including study design, research coordination, data collection, and all statistical analyses. All manuscripts were written by Dilan Patel and co-authored by members of his thesis advisory committee, including primary thesis supervisor, Dr. Jeffrey Perry, thesis co-supervisor, Dr. Monica Taljaard and Dr. Krishan Yadav. Other members included in these manuscripts are Dr. Daniel James, who is an emergency physician affiliated with anesthesia and pain medicine, and Dr. Michael Hickey, who provided invaluable feedback and consultation throughout the postal survey procedure based on prior experience. The research in this thesis was made possible by Angela Marcantonio, research facilitator with the Department of Emergency Medicine, who provided support with ethics submission. The research in this thesis was approved by the Ottawa Health Science Network Research Ethics Board. Carolyne Kennedy and members of the Patel family assisted with logistical matters related to the postal survey and data organization.

ABSTRACT

Background:

Current recommended treatment options for primary headache disorders are suboptimal in that effective pain relief is untimely and associated with side effects.

Objective:

The primary aim of this thesis was to evaluate the effectiveness and attitudes towards an alternative treatment option, the sphenopalatine ganglion (SPG) block which belongs to a class of procedures known as peripheral nerve blocks (PNBs).

Methods:

We conducted a systematic review and meta-analysis studying the effectiveness of PNBs for the treatment of primary headache disorders. We also conducted a national postal survey among Canadian emergency physicians to identify current practice patterns and perspectives on PNBs.

Results:

We found PNBs are effective for rapid pain relief compared to placebo at 15 minutes (MD = -1.17; 95% CI: -1.82 to -0.51) and 30 minutes (MD = -0.99; 95% CI: -1.66 to -0.32). Only 55.6% of physicians have experience with PNBs (95% CI: 0.48 to 0.65) and we discovered the SPG block is the least commonly practiced type of PNB; the majority of physicians believe these procedures are safe (85%) and effective (55.1%). A future trial is needed to compare the SPG block against standard treatment.

Conclusion:

The SPG block may be used as an adjunct therapy for faster effective pain relief. Current physicians would consider PNBs as a first-line alternative given evidence from a future trial. A future trial is needed to compare the SPG block against standard treatment.

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LIST OF ACRONYMS AND ABBREVIATIONS

CCFP-EM: Canadian College of Family Physicians; Special Competency in Emergency Medicine

CI: Confidence Interval

ED: Emergency Department

EP: Emergency Physician

FRCPC: Fellow of the Royal College of Physicians and Surgeons of Canada

GONB: Greater Occipital Nerve Block

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

ICHD: International Classification of Headache Disorders

IHS: International Headache Society

IQR: Interquartile Range

IV: Intravenous

MD: Mean Difference

NRS: Numerical Rating Scale

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

PNB: Peripheral Nerve Block

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

RCT: Randomized Controlled Trial

SD: Standard Deviation

SPG: Sphenopalatine Ganglion

VAS: Visual Analogue Scale

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Chapter 1: Introduction

1.1 Introduction

Primary headache disorders are one of the most common disorders of the nervous system; although non-life threatening, primary headaches are highly prevalent and cause significant pain and disability to the general population. The most common primary headaches are tension, migraine and cluster headaches. According to the World Health Organization (WHO), the global prevalence of headache is approximately 50% and predominantly affects adults aged 18 and over.[1] Headache is a common emergency department (ED) presentation accounting for 1 to 4% of all visits.[2–6] Clinicians are often faced with the challenge of the optimal management of headache presentations given the diversity of recommended drug therapies.

Recommended first-line drug therapies include oral or intravenous non-steroidal anti-inflammatory drugs (NSAIDs), dopamine antagonists and triptans.[7] Alternative treatment options include a class of treatments known as peripheral nerve blocks (PNBs). These bedside procedures involve injecting a small amount of anesthetic to freeze local target points. The exact mechanism of action is unclear; however there is evidence to support that these procedures break the pain cycle which may correlate with physiological factors involved in the production of chronic pain.[8] Common PNBs for headache management include the greater occipital nerve block, the sphenopalatine ganglion (SPG) block and trigger point injections. The most appealing technique is the SPG block due to its ease of administration such as simple intranasal droplets of lidocaine (a local anesthetic) commonly referred to as the Method of Barre, which does not require an injection.[9–11]

1.2 Rationale

Headache presentations to the ED can be challenging for clinicians. Aside from identifying the cause of headache and ruling out serious or life-threatening etiologies, the optimal management of primary headache disorders remains unclear. The goal for emergency physicians is to accurately diagnose headache and rapidly treat pain. Recommended drug therapies are effective; however, the time to effective pain relief is often suboptimal and may be associated with side effects. The effectiveness of alternative treatments, such as PNBs, for the treatment of primary headaches has been studied in clinical trials; however, the quality of evidence is low and there is insufficient evidence to support their use as a first line treatment option. Currently, the Canadian Headache Society provides a weak recommendation for intranasal lidocaine due to low-quality evidence from small existing trials.[12] The American Headache Society also states there is inadequate evidence for intranasal lidocaine.[13] There is a gap in current research which speaks to the need for a future high quality, randomized controlled trial (RCT) that evaluates the effectiveness of the SPG block for the treatment of primary headache disorders against current standard of care. A systematic review to integrate evidence from any existing trials testing effectiveness of PNBs for primary headaches as well as a survey of emergency physicians across Canada to determine current usage and perspectives towards PNBs are important foundational elements to inform the design of such a trial.

1.3 Thesis Goals and Overview of Chapters

The main goals of this thesis are to gain an in depth understanding of the effectiveness of PNBs to treat primary headache disorders based on current evidence and obtain consensus about current attitudes and perspectives among emergency physicians about this alternative treatment method. Secondary goals of this thesis are to identify important design features for a future RCT

to study the SPG block for treating headache disorders in the ED, including i) the optimal comparator; ii) the optimal time to reassess pain; and iii) the minimal clinically important difference (MCID) to inform sample size calculations for a future trial.

1.3.1 Overview of Chapter 1: Introduction

The introductory chapter provides i) a brief overview and rational for researching headache management in the ED, ii) the thesis goals and objective and iii) an overview of each chapter.

1.3.2 Overview of Chapter 2: Background

Chapter two provides a thorough review of the epidemiology and etiology of primary headache disorders. This chapter also explores the diagnosis and management of headaches in the ED setting including current recommended drug therapies and background information on PNBs.

1.3.3 Overview of Chapter 3: Systematic Review & Meta-Analysis

This chapter is a published manuscript of a systematic review and meta-analysis, titled: "Effectiveness of Peripheral Nerve Blocks for the Treatment of Primary Headache Disorders: A Systematic Review and Meta-Analysis.[14]" The main goal of this manuscript was to synthesize evidence from existing RCTs about the effectiveness of PNBs for the treatment of primary headache disorders. We aimed to investigate treatment effects on i) pain scores for PNBs compared to placebo or standard therapy within 120 minutes; ii) pain at 2 to 72 hours; iii) adverse events associated with PNBs and iv) the need for rescue medications and any readmission to the ED or clinic for headache within 72 hours.

Manuscript: Patel D, Yadav K, Taljaard M, Shorr R, Perry JJ. Effectiveness of Peripheral Nerve Blocks for the Treatment of Primary Headache Disorders: A Systematic Review and Meta-Analysis. *Annals of Emergency Medicine*. 2021;0(0). doi:10.1016/j.annemergmed.2021.08.007

DOI: **https://doi.org/10.1016/j.annemergmed.2021.08.007**

1.3.4 Overview of Chapter 4: National Postal Survey

This chapter is a manuscript reporting the results from a national survey of Canadian emergency physicians. The goals of this study were to i) determine common drug therapies used for primary headaches in the ED setting; ii) determine the prevalence of PNB use among emergency physicians in Canada, and iii) determine the proportion of physicians who agree with certain design features of a future trial studying the SPG block compared to standard treatment.

Manuscript: Patel D, Taljaard M, Yadav K, James D, Perry JJ. Current Practice for Primary Headache Disorders and Perspectives on Peripheral Nerve Blocks Among Emergency Physicians in Canada: A National Survey. *Headache*. Accepted, February 28, 2022. In press.

1.3.5 Overview of Chapter 5: Methodology of Postal Surveys

This chapter is a manuscript reporting results from a preplanned RCT embedded within a national survey (see Chapter 4), to determine if there was a difference in response rates in letters which were hand-signed compared to letters which were electronically signed. Findings from this analysis provide recommendations and guidance for future postal surveys as to whether the labour and time involved with personalizing letters through hand-signatures is beneficial in terms of an increased response rate.

1.3.6 Overview of Chapter 6: Discussion

This chapter is a discussion which summarizes key findings from chapters 3 to 5 and provides future directions and next steps for research in the area of headache management.

1.4 Impact of Thesis

The burden of headache disorders on Canadians is an important issue which causes significant disability as well as loss of productivity. The three main impacts of this thesis are 1) synthesizes evidence from RCTs for PNBs to treat headaches in order to highlight estimated effect and to highlight how existing trials may be improved; 2) describes current attitudes of emergency physicians towards the use of PNBs and how headaches are managed in general across Canadian EDs; and 3) provides important design features of a future multicenter RCT with robust methodology based on results from chapters 3 and 4. This may ultimately lead to practice changing recommendations for emergency physicians and improve the quality of life of patients in their care.

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Chapter 2: Background

2.1 Overview

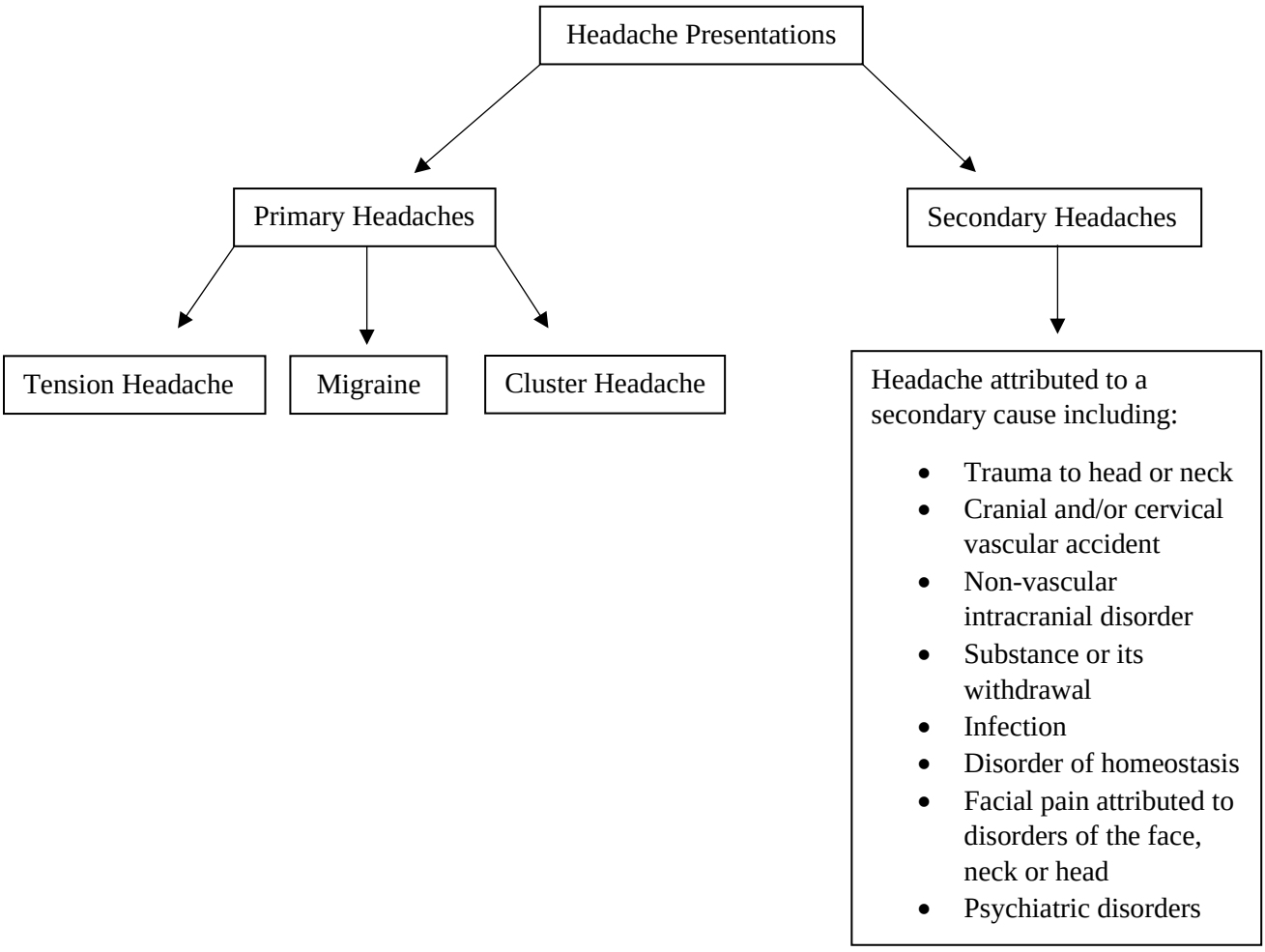
This chapter provides an in-depth background on the classification, epidemiology, and burden of primary headache disorders in the context of emergency medicine. Current recommended treatment options for primary headache disorders in the emergency department (ED), including their known side effects are reviewed. Alternative treatment options, namely peripheral nerve blocks, are outlined in detail including their modes of administration, localization with respect to anatomy and physiology as well as their advantages compared with current treatment options.

2.2 Headache Classification & Epidemiology

2.2.1 Primary Headaches

Headaches are divided into primary and secondary and are categorized by the third edition of the International Classification of Headache Disorders (ICHD-3).[1] Primary headaches have no underlying serious identified cause and include tension headache, migraine and trigeminal autonomic cephalalgias (of which cluster headache is the most prevalent). In contrast, secondary headaches are due a known causative disorder (see Figure 2.1).

Figure 2.1 Abbreviated Classification of Headaches According to the ICHD-3



ICHD-3: International Classification of Headache Disorders, third edition[1]

2.2.2 Tension Headache

Tension headaches are the most prevalent primary headache with a global prevalence of 42%.[2,3] This form of headache is described as bilateral headache which does not worsen with physical exertion and not associated with nausea and vomiting.[4] Tension headaches may be episodic, lasting from 30 minutes to 7 days, or chronic, continuously lasting for hours for 15 or more days a month for at least 3 months.[5]

2.2.3 Migraine

Migraines are one of the most common benign disabling brain disorders, affecting 14.7% of adults globally and ranks as the third most common disease in the world and the seventh most disabling disease in terms of years lived with disability.[6,7] An estimated 8.3% of Canadians (2.7 million) reported a prior diagnosis of migraine by a health professional with females being more affected than males.[8] According to a population-based survey, the prevalence of migraine was 8-10% in males and 23-26% in females.[9] Migraines are associated with variable levels of pain and discomfort and its etiology is thought to be genetically or environmentally driven.[10] Migraine headaches are typically associated with pain which usually lasts from 4-72 hours and is associated with unilateral, pulsating headaches which are worsened by physical activity and associated with nausea and vomiting, photophobia (increased sensitivity to light) and/or phonophobia (increased sensitivity to sound) with or without an aura (i.e. transient neurological symptoms resolving within 1 hour).[4,11]

2.2.4 Trigeminal Autonomic Cephalalgias – Cluster headache

Cluster headaches are the most common form of a group of headaches known as the trigeminal autonomic cephalalgias and are the least common primary headache disorder, with a prevalence of less than 1% that predominantly affects males.[12,13] Cluster headaches are characterized by i) at least five attacks; ii) severe, unilateral orbital/supraorbital/temporal pain lasting from 15 to 180 minutes; iii) at least one of the following: conjunctival injection or lacrimation; nasal congestion and/or rhinorrhea; eyelid edema; forehead and facial sweating; miosis and/or ptosis and/or a sense of agitation or restlessness; iv) frequency of attacks between one every other day to eight attacks per day and v) not better accounted for by another ICHD-3 diagnosis.[1]

2.2.5 Secondary Headaches

Secondary headaches differ from primary subtypes in that the cause of the headache arises from a known source. So when a new headache arises for the first time in close temporal relation to another disorder known to cause headache, the new headache is classified as a secondary disorder attributed to the causative disorder.[1] Examples of secondary headaches include intracranial neoplasia (brain tumor), blunt trauma to the head or neck, subarachnoid hemorrhage (intracranial bleeding), cerebral infarction, cervical vascular disorder, substance use or withdrawal, infection, or psychiatric disorders (Figure 1).[1] Secondary headaches often have a serious or life-threatening etiology which is the underlying cause of the headache. It is therefore important for emergency physicians to rule out secondary headaches in patients presenting with headache.

Table 2.1 Diagnostic criteria for primary headache disorders according to the International Classification of Headache Disorders 3rd edition[1]

Primary Headache Type	Diagnostic Criteria
Tension **Infrequent episodic tension-type headache**	1. At least 10 episodes of headache occurring on 1-14 days/month on average for >3 months (≥12 and <180 days/year) and fulfilling criteria B-D 2. Lasting from 30 minutes to 7 days 3. At least two of the following four characteristics: 1. bilateral location 2. pressing or tightening (non-pulsating) quality 3. mild or moderate intensity 4. not aggravated by routine physical activity such as walking or climbing stairs 4. Both of the following: 1. no nausea or vomiting 2. no more than one of photophobia or phonophobia 5. Not better accounted for by another ICHD-3 diagnosis.
Migraine **without aura**	A) At least five attacks1 fulfilling criteria B-D B) Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)[2;3] C) Headache has at least two of the following four characteristics:

	i) unilateral location ii) pulsating quality iii) moderate or severe pain intensity iv) aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs) D) During headache at least one of the following: nausea and/or vomiting photophobia and phonophobia E) Not better accounted for by another ICHD-3 diagnosis
with aura	A. At least two attacks fulfilling criteria B and C B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal C. At least three of the following six characteristics: 1. at least one aura symptom spreads gradually over ≥5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis.
chronic	A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura* C. On ≥8 days/month for >3 months, fulfilling any of the following 1. criteria C and D for 1.1 *Migraine without aura* 2. criteria B and C for 1.2 *Migraine with aura*

	3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative B. Not better accounted for by another ICHD-3 diagnosis
Cluster	A. At least five attacks fulfilling criteria B-D B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)1 C. Either or both of the following: 1. at least one of the following symptoms or signs, ipsilateral to the headache: – conjunctival injection and/or lacrimation – nasal congestion and/or rhinorrhea – eyelid oedema – forehead and facial sweating – miosis and/or ptosis 2. a sense of restlessness or agitation D. Occurring with a frequency between one every other day and 8 per day2 E. Not better accounted for by another ICHD-3 diagnosis.

2.3 Headache Burden of Disease

2.3.1 Headache Disability

The pain from primary headache disorders has the potential to be debilitating and have a tremendous negative impact on individuals. The burden of headache not only translates to physical pain on individuals but also to a societal and economical impact in terms of loss of productivity due to time off from work and costs to the healthcare system from ED utilization of resources. According to the Global Burden of Disease, migraine alone was the second most prevalent cause of disability in the world and the third-highest cause of disability in both males and females under the age of 50.[1,14] The optimal treatment and management of headache in the ED is an important issue.

2.3.2 Socioeconomic Burden of Headache

A high proportion of those suffering from migraine report debilitating pain which impedes activities of daily living and often results in days off from work. According to data from migraine

studies, approximately 28 million Americans and 5.8 million Britons are current sufferers of migraine; 50% of these cases report their migraine is debilitating and impedes their activities of daily living.[15–17] According to another study, 5.7 working days were lost per year for every working or student migraineur.[16]

2.3.3 Costs – ED Utilization

Current management of severe primary headache presentations to the ED can be considered costly and burdensome to the Canadian healthcare system as a result of tests ordered and time waiting. Between 2004 and 2013, the total adjusted incremental direct health care cost due to migraine alone was 9.21 billion dollars per year in the United States.[18,19]

Due to an ongoing ED overcrowding issue, which is a global concern and considered a national crisis in some countries, patients with serious or life-threatening illnesses may be left waiting to be seen by physicians with an increased average length of stay. This has several consequences including patients not receiving time-sensitive interventions, treatments for severe infections or advance diagnostic imaging.[20] Furthermore, there is an association between ED overcrowding and an increase in 30-day adverse events, where one study found a 10% increase in ED bed occupancy resulted in a 3% increase in death and hospital admission.[21] The primary goal for the ED in communities is the treatment of seriously ill and injured patients.[22] The treatment of non-life threatening conditions such as primary headache presentations to the ED is important to treat rapidly; this is beneficial for both patients and ED flow. This would ultimately result in patients being discharged home from EDs faster and reduce overcrowding issues which are common in North America.

Headache management in the ED is costly due to the challenges involved with diagnosis, ordering of tests and time to effective pain relief with minimal risk for relapse. After ruling out

serious etiologies, the most rapid and effective treatment which alleviates pain and results in a faster and safer discharge home for benign headache patients in the ED is beneficial for both the healthcare system and patients.

2.4 Headache Diagnosis

Headache presentations to the ED are often complex and require thoughtful consideration by emergency physicians. Primary headaches account for 1-4% of all emergency department visits.[23–27] Although 96% of these presentations are benign and non-traumatic in nature, 1-3% can be life-threatening in forms such as subarachnoid hemorrhage (SAH) (i.e. a bleeding brain aneurysm).[28–30] The main challenge with accurate diagnoses of primary headaches are the complex and restrictive diagnostic criteria for the ICHD-3. As seen in Figure 2.1, there are specific and lengthy criteria for each primary headache; each type can present with various subtypes such as infrequent episodic or frequent episodic or chronic tension headache.[1] The specific cut-offs for certain diagnostic criteria make the ICHD-3 restrictive and some of the time, not practical for real time use in emergency medicine but rather useful for headache specialists to classify patients.

The most common presentations to the ED for headache are likely more severe cases such secondary headaches, and primary headaches including migraine, chronic migraine, and trigeminal autonomic cephalalgias such as cluster headache. The most disabling form of primary headache which constitutes the most prevalent presentation to the ED are migraines.[31–34] Given the fast paced ED environment, an emergency physician's primary focus is to identify and treat serious or life-threatening ailments as quickly and effectively as possible. According to an ED based study, 95% of patients meet IHS criteria for migraine; however, only 32% of cases were diagnosed as such, while 59% were diagnosed as cephalgia or headache not otherwise stated. These findings hold true in other studies where accuracy of correct diagnosis is low, ranging from 15 to 32%.[31–34]

2.5 Current Drug Therapies for Headache Management in The Emergency Department

Current recommend treatment options for primary headaches in the ED are diverse. These include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, dopamine antagonists, and opioids. Administration and selection of medication varies among emergency physicians and is usually based on experience, training, and the severity of headache. Treatment options are typically divided into first-line, which is the first choice of medication to alleviate headache pain, and second-line, if first-line treatment options are unsuccessful.

First-line treatment options for primary headaches include NSAIDs such as ketorolac, acetaminophen, antidopaminergic agents such as metoclopramide, prochlorperazine or haloperidol, oxygen therapy for cluster headaches and corticosteroids such as dexamethasone for reduction of migraine recurrence.[35] Other medication options which are not recommended as first-line treatment options however may be used frequently are IV fluids, antiemetics such as dimenhydrinate or ondansetron, abortive therapy such as triptans, other butyrophenones such droperidol, ergotamine, magnesium, sodium valproate and opioids.[35,36]

Current second-line treatment options for primary headaches in the ED include ketamine propofol, opioids and peripheral nerve blocks.[35,36]

Table 2.2 Current Treatment Options for Primary Headaches in the Emergency Department*

First -Line				
Drugs	**Class**	**Recommendation[a]**	**Primary Headache**	**Side Effects**
IV ketorolac, ibuprofen, naproxen; IM diclofenac	NSAIDs	C	Tension, Migraine	Acute kidney injury, nausea, and dyspepsia, temporary platelet dysfunction
PO/IV acetaminophen	Analgesic	C	Tension, Migraine	Rare: liver toxicity in cases of overdose/poisoning

IV/PO metoclopramide; IV/PO prochlorperazine; IV/PO chlorpromazine	Dopamine antagonist; anti-emetic	B	Migraine	Drowsiness, orthostatic hypotension, and akathisia
PO diphenhydramine	Antihistamine	Used for adverse drug reactions (akathisia)	Tension, Migraine	Drowsiness, dizziness, nausea, vomiting
IM/IV dexamethasone, IV methylprednisolone	Corticosteroid; anti-inflammatory	Used to reduce migraine recurrence	Migraine	Dizziness, nausea, vomiting
PO/IV Dimenhydrinate, ondansetron	Antiemetic	U	Migraine	Drowsiness, dryness in mouth, constipation, blurred vision
SC sumatriptan; IN zolmitriptan	Anti-migraine; serotonin agonist ; triptan	B	Cluster, migraine	Non-cardiac chest pain, flushing, paresthesias, and worsening of headache
Oxygen therapy	Oxygen	For cluster headache	Cluster	Rare
Second-Line				
Therapy	**Class**	**Recommendation[a]**	**Side effects**	
IV ketamine	NMDA receptor antagonist; analgesics; dissociative hallucinogens	U	Fatigue, insobriety, hypertension, confusion	
IV propofol	Sedative; hypnotic	U	Hypotension, respiratory depression	
PO/IV tramadol, morphine, hydromorphone, fentanyl	Opioids	D	Progression of headache, constipation, nausea or vomiting, sedation, dizziness, physical dependence	
Occipital nerve block, sphenopalatine ganglion block, trigger point injection	Peripheral Nerve Blocks	C	Injection site pain, burning sensation	
Other drugs				
Therapy	**Class**	**Recommendation[a]**	**Side effects**	
IV Magnesium sulfate	Electrolyte replenisher	U	Respiratory depression, hypotension, weakness, confusion, anxiety, heart disturbances, drowsiness	
IV Sodium valproate	Anti-migraine; anticonvulsant	C	Headache, abdominal pain, somnolence, dizziness	
IV droperidol, IV haloperidol	Anti-psychotic; butyrophenones	C	Akathisia, QTc prolongation	

IV fluid bolus	Crystalloids	For dehydration and/or nausea and vomiting	Volume overload
IV/SC Dihydroergotamine (DHE)	Ergotamine	D	Chest pain, palpitations, cough, fever, sneezing, itchiness

[a]Recommendation level: Must offer (level A) ; Should offer (level B) ; May offer and may avoid (level C) ; Avoid (level D) ; No recommendation (level U)
IM: Intramuscular; IN: Intranasal; IV: Intravenous; PO: Oral; SC: subcutaneous
*Adapted from Long and Koyfman and Orr et al.[35,37]

There is some overlap in the management of primary headache disorders in the ED while some medications should only be used for certain primary headache subtypes.

Tension headache is the most common primary headache disorder but patients with this disorder are also the least likely to present to the ED due to mild pain. Patients often treat tension headache using over the counter pain relief medications. In the ED setting, first-line treatment options for tension headache include acetaminophen, ibuprofen, naproxen, and diclofenac (Table 2.2).[38–40]

Migraine presentations to the ED are the most prevalent and first-line treatment options include dopamine antagonists, NSAIDs and triptans (Table 2.2).[37,38,41] Migraines are typically treated using combination therapies, often known as migraine cocktails, which involve NSAIDs in combination with triptans, dopamine antagonists or acetaminophen and are more effective than monotherapies.[42]

Recommended first-line treatment options for cluster headaches include oxygen therapy and triptans (Table 2.2).[38,43]

2.5.1 Issues With Current Drug Therapies

While many of the aforementioned drug therapies are recommended and demonstrated to be effective, they may be considered suboptimal in the ED setting due to slow time to effective pain relief, associated with rare but significant side effects[44,45] and often require combination

treatment with other medications such as NSAIDs (e.g. ketorolac) or repeat dosing. Previous studies have shown that those treated ineffectively for headache disorders may be at increased risk of developing chronic migraine or may relapse into a full migraine post initial treatment thus resulting in repeat ED visits.[46]

Time to effective pain relief for current recommended drug options may be considered suboptimal. For example, NSAIDs have demonstrated a 57% decrease in median pain score at 1 hour using 30 mg of IV ketorolac[47,48]; dopamine antagonists such as metoclopramide have shown an estimated 34% to 46% effectiveness at 30 to 60 minutes in small prospective randomized, double-blind, placebo-controlled trials.[47,49,50] Chlorpromazine was shown to be 80% effective at 1 hour in a small, randomized double-blind placebo-controlled trial.[47,51] A faster and more effective treatment option within shorter time frames than current recommended treatments would be more beneficial for patients with headache pain in the ED.

Side effects for drug therapies are rare but significant and range from mild to severe symptoms (Table 2.2). For example, in first-line treatment options, NSAIDs such as ketorolac are commonly used for migraine and are associated with acute kidney injury, nausea and dyspepsia, although the risk is low.[38] For dopamine antagonists, such as metoclopramide, prochlorperazine and chlorpromazine, common side effects include drowsiness, orthostatic hypotension and akathisia. Since akathisia is a common side effect, diphenhydramine is often administered in combination with dopamine antagonists as a preventative measure for akathisa.[38] Another example is the use of haloperidol, which is also a dopamine antagonist classified as an anti-psychotic and known to cause extrapyramidal symptoms such as acute dystonia (involuntary contraction of muscles of the face and neck), akathisia (restlessness), neuroleptic malignant syndrome (high fever, irregular or accelerated heartbeat, high or low blood pressure, sweating, altered mental

status), and anticholinergic effects (dry mouth, confusion, hallucinations, constipation, urinary retention, increased heart rate, dilated), and serious side effects with chronic use including parkinsonism (tremors, impaired speech, muscle stiffness), tardive dyskinesia (repetitive and uncontrolled jerking movements in the face and neck).[53,54] Common side effects for triptans include noncardiac chest pain, flushing, paresthesia, and worsening of headache.[38] Triptans have several contraindications including those with a history of coronary artery disease, history of stroke, peripheral vascular disease and uncontrolled high blood pressure.[52]

A controversial medication option is the use of IV opioids for the treatment of benign primary headaches in the ED. According to a US-based survey, opioids were administered or prescribed in over 50% of migraine visits in the ED.[55] Many societies and committees recommend against using opioids for migraine and other primary headaches. Opioids are disadvantageous as a treatment option since their use has been associated with increased frequency of recurrent ED visits, can impair the effectiveness of other migraine treatments, promotes chronic migraine and medication overuse headache and is associated with more psychiatric disorders when dependence is built on opioid use.[36,56] The prevalence of administration of prescription opioids as a first-line treatment for primary headache disorders in Canadian EDs is currently unknown. Although IV opioids may be safe when administered in a monitored setting, their use for primary headaches are not recommended due to risks of addiction, side effects and lower efficacy than other treatments; however there are circumstances where their use is appropriate as a second-line treatment option.[35,36]

2.6 Alternative Treatment Options

2.6.1 Peripheral Nerve Blocks

An alternative treatment which is currently understudied and not widely used for the treatment of headache are peripheral nerve blocks (PNBs). Most PNBs are not recommended due to insufficient or low-quality evidence to support their use. The main PNBs used for benign headaches in the ED are the occipital nerve block, sphenopalatine ganglion (SPG) block or trigger point injections. The main difference between the PNBs are the route of administration and target location for anesthesia. The exact mechanism for how PNBs operate to alleviate pain is unclear; however, there is evidence to support directly blocking nerves responsible for pain from various regions correlate to breaking the pain cycle for both peripheral and central sensitization.[57–60]

Currently, the effectiveness of PNBs have been studied in a limited number of RCTs for various primary headache disorders and their effectiveness for timely pain relief is uncertain and therefore these procedures cannot be recommended as a first-line alternative. For example, currently the Canadian Headache Society lists intranasal lidocaine as an alternative; however is recommended with "weak: low-quality evidence".[61,62]

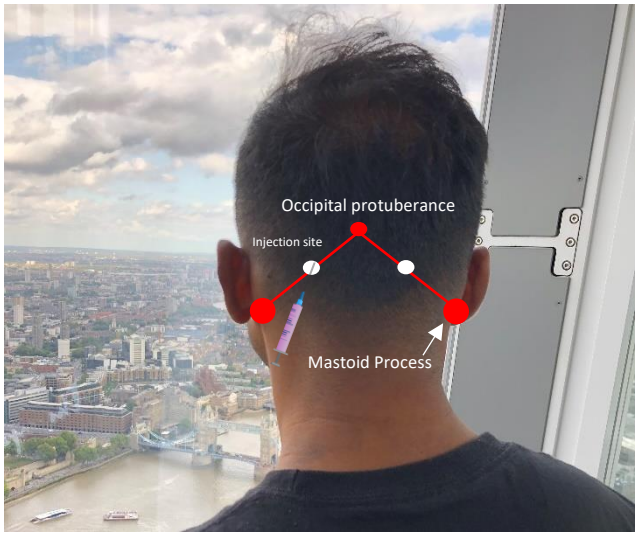
2.6.2 Occipital Nerve Block

The occipital nerve block is a minor bedside procedure which is increasingly being used to alleviate benign headache pain in the ED. The occipital nerve block is commonly administered to the greater occipital nerve; however, can also be administered to the lesser occipital nerve. The greater occipital nerve is the primary sensory nerve of the occipital region and is derived from C_2 dorsal root as well as the C_3 segments of the spinal cord.[63,64] The greater occipital nerve is accessible from the posterior part of the head.

The greater occipital nerve block is hypothesized to alleviate pain by operating through the trigeminocervical complex which is responsible for causing migraine pain.[65] Clinical evidence for this pathway is limited. However, it is believed that blocking the greater occipital nerve can relieve pain associated with migraine since the greater occipital nerve terminates in the trigeminocervical complex.[64,65] Using local anesthetics to reduce the sensation of trigeminal and cervical afferents, which converge to the trigeminocervical complex along the course of the greater occipital nerve and its cervical origin has shown to be effective in headache pain relief.[66]

The greater occipital nerve block is achieved by identifying landmarks on the patient's head such as the occipital protuberance and mastoid process; using these landmarks, the occipital nerve is located, and an injection of local anesthetic is administered using a fanning technique (Figure 2). The greater occipital nerve block has shown favourable results in clinical trials and clinical practice; however, the evidence is limited and deemed low quality.[66]

Figure 2.2 Anatomical landmarks for greater occipital nerve block



2.6.3 Sphenopalatine Ganglion Block

The sphenopalatine ganglion (SPG) block involves blocking the sphenopalatine ganglion (also known as the pterygopalatine ganglion). The SPG block is the most versatile and can be blocked using a variety of different methods.

2.6.3.1 Anatomy & Pathophysiology

The SPG is extracranial and is parasympathetic with multiple neural connections. The SPG is housed under a thin (1-2 mm) layer of mucosa in the pterygopalatine fossa and suspended from the maxillary nerve.[67] The SPG receives sensory, parasympathetic and sympathetic projections from the nasopalatine nerve, superior and inferior lateral nasal branches and pharyngeal branch of the maxillary nerve.[67]

Since primary headache disorders are associated with parasympathetic activation (nasal congestion, lacrimation, etc.), blocking the sphenopalatine ganglion seems like a viable target location to alleviate pain.[44] The sphenopalatine ganglion plays an important role in the pathophysiology of headaches with respect to the trigemino-autonomic reflex; various primary headache triggers brain areas responsible for activating the trigemino-autonomic reflex.[44,67] The SPG is responsible for expressing cranial autonomic symptoms which are commonly seen in trigeminal autonomic cephalalgias such as cluster headache. This explains why blocking the SPG may be successful and may contribute to effective pain relief of other primary headache disorders such as migraine and cluster headache.[67]

2.6.3.2 Modes of Administration

SPG blocks are the most versatile PNB due to the extracranial location of the sphenopalatine ganglion. The SPG may be blocked using various methods such as cotton tip

applicators, simple intranasal droplets of lidocaine or transnasal devices such as the Tx360® device.[44,68]

The SPG block is the most appealing form of PNB due to its simplicity and ease of administration. The least invasive method of blocking the SPG has been achieved using intranasal droplets of lidocaine, often referred to as the Method of Barre.[69–71] This procedure involves having the patient lie in a supine position with the head hanging from the edge of the bed, turning the head 30^0 to the side with the headache and adding droplets of an anesthetic, usually lidocaine, intranasally (Figure 3).[70]

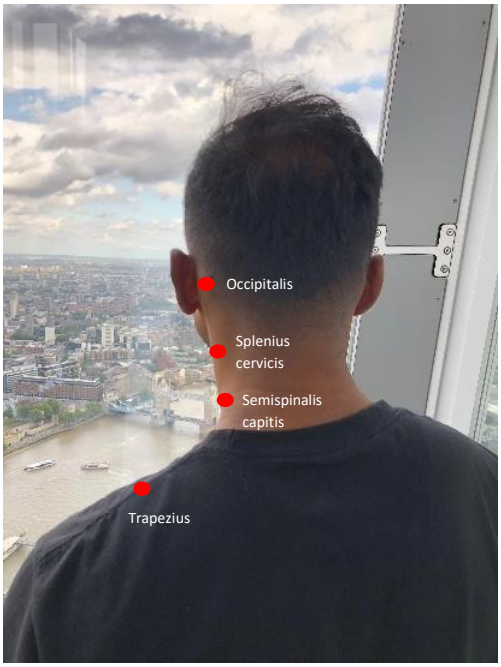
Figure 2.3 Sphenopalatine ganglion block - Method of Barre

2.6.4 Trigger Point Injection

Trigger point injections have been used for treating pain associated with primary headache disorders. Trigger point injections operate by alleviating myofascial pain which is often present with primary headache disorders.[72,73] This procedure involves injecting a local anesthetic at common sites such as the trapezius and posterior cervical paraspinal muscles (Figure 3).[74,75]

Trigger point injections are most commonly used for chronic tension headaches and chronic migraine.[73] There is very limited data available on this procedure to support their use despite practitioners describing them as beneficial for their patients.[72]

Figure 2.4 Common trigger point sites for injection



2.6.5 Choice of Anesthetic

Commonly used anesthetics for PNBs are lidocaine and bupivacaine. The main difference is the duration and speed of onset. Lidocaine has an onset of action between 4 and 8 minutes and lasts between 1 and 2 hours while bupivacaine has a slower onset of action between 8 and 12 minutes and a longer duration of action lasting between 4 and 8 hours.[19,76] Lidocaine is typically administered in volumes ranging from 0.1 to 2 mL; bupivacaine ranges from 0.3 to 6 mL.

2.7 Conclusion

The optimal treatment of primary headache disorders in the ED remains an important area of research. Current standards of care are effective; however, may be considered suboptimal due to slow effective pain relief, unpleasant side effects and unfavourable route of administration. The

SPG block appears to be a viable alternative if proven to provide a faster time to effective pain relief with no serious side effects. The subsequent chapters will provide evidence on the effectiveness of PNBs for primary headache disorders by i) synthesizing results from existing trials to determine the estimated effect and ii) a national survey will be conducted to determine current practice of primary headache disorders in Canadian EDs and to determine emergency physician perspectives and attitudes towards PNBs. These two major studies provide important foundational elements towards designing a future trial to study the SPG block against current standard of care to inform decisions about potentially safer and more effective strategies for treating primary headache disorders in the ED.

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Chapter 3: Effectiveness of Peripheral Nerve Blocks for The Treatment of Primary Headache Disorders: A Systematic Review And Meta-Analysis

Authors:
*Dilan Patel[1,2], BSc
**Krishan Yadav[2,3]
**Monica Taljaard[1,2]
Risa Shorr[4], MLS
Jeffrey J. Perry[1,2,3], MD, MSc

Author Affiliations:
1. School of Epidemiology and Public Health, University of Ottawa, K1G 5Z3 Ottawa, Ontario, Canada.
2. Ottawa Hospital Research Institute, ON K1Y 4E9 Ottawa, Ontario, Canada
3. Department of Emergency Medicine, University of Ottawa, Ontario, Canada
4. Learning Services, The Ottawa Hospital, Ottawa, Ontario, Canada

*Corresponding Author
Dilan Patel
ORCID: 0000-0002-2921-0576
Clinical Epidemiology Program, Department of Emergency Medicine
Ottawa Hospital Research Institute

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This manuscript was conceptualized by DP, KY and JJP. RS generated our electronic search strategy. DP and KY curated the data and DP carried out the investigation, visualization, and the formal analysis. Statistical analysis was conducted by DP and MT. This manuscript was supervised by JJP and MT. KY validated the data. The original draft was written by DP. The writing, reviewing, and editing of this manuscript was conducted by DP, KY, MT, RS and JJP.

3.1 Abstract

Objective:

Primary headache disorders are prevalent and account for 2% of all emergency department (ED) visits. Current treatment options are effective; however, time to pain relief is suboptimal. Alternatives such as peripheral nerve blocks (PNBs) have shown promising results. The objective of this systematic review is to examine the effectiveness of PNBs for timely pain relief.

Methods:

We searched Ovid MEDLINE, EMBASE, Web of Science Core Collection and the Cochrane Central Register of Controlled Trials and included randomized controlled trials comparing PNBs to placebo or active therapy. The primary outcome was pain within 120 minutes. Secondary outcomes were pain after 120 minutes, adverse events, need for rescue medications and relapse of headache. Two reviewers screened and extracted data independently; mean differences (MDs) were calculated, and results were pooled using a random-effects model.

Results:

11 studies met our eligibility criteria (n = 860) of which 9 were included in the meta-analysis. Pain scores were significantly lower in patients treated with PNBs than placebo at 15 minutes (MD = -1.17; 95% CI: -1.82 to -0.51) and 30 minutes (MD = -0.99; 95% CI: -1.66 to -0.32) and no serious adverse events were reported. Pain scores for PNBs versus active therapy and secondary outcomes were not pooled due to clinical heterogeneity.

Conclusions:

Our review shows PNBs are effective as a rapid treatment option when compared to placebo; however, we were unable to assess effectiveness against standard treatment. Emergency physicians should consider PNBs as an adjunct therapy for patients with primary headache disorders.

Key Words: Primary headache, tension headache, cluster headache, migraine, peripheral nerve block, greater occipital nerve block, sphenopalatine ganglion block, intranasal lidocaine, trigger point injection, systematic review

Abbreviations: CI = confidence interval, ED = emergency department, PNB = peripheral nerve block, SPG = sphenopalatine ganglion block, MD = mean difference, SMD = standardized mean difference, PRIMSA = preferred reporting items for systematic review and meta-analysis. RCT = randomized controlled trial, NSAID = nonsteroidal anti-inflammatory drugs, VAS = visual analogue scale, NRS = numerical rating scale, SD = standard deviation

3.2 Introduction

3.2.1 Background

Headache disorders are one of the most common disorders of the nervous system which affect majority of the population at some point in their lifetime.[1,2] Headaches cause significant disability which negatively impacts quality of life due to burden of pain and on a societal level in terms of loss in productivity.[3,4] According to the International Classification of Headache Disorders Third Edition (ICHD-3)[5], headaches are divided into primary and secondary classifications, with primary being non-traumatic and benign in nature and secondary headaches being attributed to a secondary cause and are potentially life-threatening. The most common types of primary headache disorders include migraine, tension headache and cluster headaches.

3.2.2 Importance

The main clinical problem for primary headache disorders in the emergency department (ED) is the relatively slow onset of current treatment options. First-line treatment options include nonsteroidal anti-inflammatory drugs (NSAIDs), dopamine antagonists, and triptans among others.[6,7] While recommended, these first-line agents may take time to be effective[8], cause side effects or fail to control the headache. Side effects for dopamine antagonists include extrapyramidal symptoms such as acute dystonia, akathisia, and anticholinergic effects.[9,10] Recent interest has grown regarding the use of peripheral nerve blocks (PNBs) such as the greater occipital

nerve block, sphenopalatine ganglion (SPG) block and trigger point injections (i.e. as a faster and more effective management of primary headaches).[6] Greater occipital nerve blocks are achieved by injecting an anesthetic with a needle towards the greater occipital nerve, which originates in the dorsal ramus of C_2 and C_3 segments of the spinal cord.[11] The SPG block is achieved by blocking the extracranial parasympathetic sphenopalatine ganglion with an anesthetic through a device or simply using techniques such as the method of Barre, where a patient lies in a supine position with their head extended 45 degrees and rotated 30 degrees ispilaterally[12–14] in preparation for intranasal droplets of lidocaine.[15,16] Trigger point injections involve an injection of a local anesthetic into various trigger points located in the head, neck and shoulder.[17] The exact mechanism for how PNBs work are unclear; however, there is evidence to suggest that local anesthetics break the pain cycle and thereby correlate with physiological factors important to the production of chronic pain.[16] Previous systematic reviews have focused on the effect of individual PNBs for specific headache subtypes. However, the time to effective pain relief at clinically important timepoints remains unclear.[18–22,23] There is uncertainty as to whether patients may be quickly and safely discharged home after receiving a PNB within 120 minutes. Time to relief of pain is important when the goal in emergency medicine is to treat acute and non-serious conditions, such as primary headache disorders as quickly and effectively as possible, while reducing IV medication and opioid use. If PNBs can be proven as effective alternatives for pain management, these procedures could be performed as first-line alternatives rather than adjunct therapy for rapid pain relief.

3.2.3 Goals of This Investigation

The primary objective of this systematic review is to evaluate the effectiveness of PNBs, including the greater occipital nerve block, the SPG block and trigger point injections for the treatment of primary headache disorders in the ED or clinic setting, for pain intensity within 120

mins when compared to placebo or other treatments. Secondary objectives are to assess pain intensity between 2 and 72 hours, adverse events and relapse of headache resulting in readmission to the ED or clinic within 72 hours.

3.3 Materials and Methods

3.3.1 Study Design and Selection of Participants

This study was registered and approved by PROSPERO (ID: CRD42020212187). The review protocol was not published, however is available upon request. This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[24] (Appendix 3A) and with guidance from the Cochrane handbook for Systematic Review of Interventions.[25]

We searched Ovid MEDLINE, EMBASE, Web of Science Core Collection and the Cochrane Central Register of Controlled Trials from inception until November 24th, 2020. We scanned the reference lists of included studies and relevant reviews identified through the search. Our search strategy was developed with a health sciences librarian and subsequently peer reviewed by a second research librarian as per Peer Review of Electronic Search Strategies (PRESS) guidelines.[26] Search items related to primary headache and type of PNBs were included using Medical Subject Headings (MeSH) and indexed terms. The full search strategy can be found in Appendix B.

We included English-language studies reporting results from randomized controlled trials (RCTs) in humans. We included studies randomizing patients of any age presenting with a primary headache disorder or benign headache not yet diagnosed. Primary headache disorders were defined according to the ICHD-3 including acute or chronic migraine, tension and cluster headaches, which account for 90% of benign headaches.[27] Headaches must be based on the ICHD-3 criteria or

equivalent, proposed by the International Headache Society. If no criteria were specified, the diagnosis of headache must be based on important characteristics of primary headache disorders. We excluded non-randomized trials, review articles and studies that assess patients with secondary headache disorders.

The results of the search strategy were uploaded to Covidence (Veritas Health Innovation, Melbourne, Australia).[28] Duplicates were removed both electronically and manually during screening. DP and KY independently screened all titles and abstracts and subsequent full texts. Any remaining discrepancies and conflicts were resolved with a third reviewer (JJP or MT).

We extracted prespecified information from included RCTs using a standardized data extraction form (Appendix 3C) created on Google Sheets © (Mountain View, California, United States). The data extraction form was piloted and we made modifications as necessary to handle the variety of data. All data were abstracted from full-texts independently by two authors (DP and KY) and conflicts were resolved by a third reviewer (JJP or MT). We converted median and interquartile ranges (IQR) to mean and standard deviation (SD), by assuming median as the mean when distribution of the data was approximately normal and dividing IQR by 1.35 to obtain the SD.[25] Trials reporting pain using the visual analogue scale (VAS) on 0-100mm scales were converted to 0-10cm to ensure comparability with trials using the numeric rating scale (NRS; 0-10 point scale). We attempted to contact corresponding authors of studies if more information was required to meet our inclusion criteria.

3.3.2 Interventions:

Patients must have been given a PNB, defined as a form of regional anesthesia near a nerve bundle with the intent to alleviate symptoms of headache. The types of PNB included in this study were the greater occipital nerve block, the SPG block (i.e., intranasal administration of a local

anesthetic), or trigger point injections. We included trials comparing the intervention to either a placebo control or standard headache therapy.

3.3.3 Outcomes:

Our primary outcome was pain intensity within 120 mins. Pain intensity must have been assessed according to a self-reported scale such as the VAS, NRS, or other permutations such as ordinal scales or rating scales within a composite measure of pain. Outcomes were collected as either continuous pain scores or as dichotomous variables defined as meeting a specified cut-off for improvement. Secondary outcomes included pain scores between 2- and 72-hours post-treatment, adverse events, the need for rescue medications and any readmission to the ED or clinic for headache within 72 hours.

3.3.4 Primary Data Analysis:

We conducted meta-analyses using a random effects model on quantitative data when at least two studies were considered sufficiently homogenous and clinically appropriate such as reporting the same outcome at a common time point using a common comparator. We separately pooled trials comparing PNB versus placebo and those comparing PNB versus standard headache therapy.

For continuous outcomes we summarized the treatment effect using mean differences (MDs) measured on a scale from 0-10cm. The VAS, measured on a scale from 0-100mm was converted to 0-10cm to be comparable with the NRS. The VAS and NRS show strong statistical correlation and can be used interchangeably as long as scores on the 0-100mm VAS are converted to the closest integer (0-10).[29] We assessed statistical heterogeneity using the I^2 statistic, where heterogeneity was considered low when $I^2 < 50\%$, moderate when I^2 is 50-75% and high when I^2

> 75%. If the I^2 statistic was considered high, we planned to explore possible sources of heterogeneity by sensitivity and sub-group analyses.

Statistical significance was assessed at the 5% level. Review Manager Version 5.4.1[30] (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for all statistical analyses.

Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2.0) tool.[31] This tool is structured in five domains for which bias in RCTs may arise. DP and KY independently ranked each domain as low risk, some concerns or high risk to determine the overall risk of bias for each study and any discrepancies were resolved by JJP or MT. Results were presented in a risk of bias summary figure using Risk-Of-Bias VISualization (robvis).[32] We planned to perform a sensitivity analysis for studies included in the meta-analysis at high risk of bias.

We rated the certainty of evidence for outcomes based on the sum of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process.[33] The strength and certainty of evidence was assessed only for studies included in the meta-analysis.

3.4 Results

Figure 3.1 demonstrates the PRISMA flow diagram for the selection process and detailed identification of included studies. A total of 1830 references were identified from our search strategy. After electronic deletion of 599 duplicates, 1231 studies were imported for screening based on the updated search strategy of databases. We excluded 1167 after reviewing titles and abstracts. 64 full-texts were assessed for eligibility and we included 11 studies in our final review.[12,15,34–42] The main reasons for exclusion were either irrelevant outcomes reported, or wrong type of headache studied.

3.4.1 Characteristics of Study Subjects

Baseline characteristics of the 11 included RCTs are summarized in Table 1. All trials were double-blind except one, which was single-blind[37] and were published between 1996 and 2020 in the United States of America (USA), Turkey or Iran. Eight trials were conducted in a ED[12,15,34,36–38,40,41] and three trials in a clinic setting.[35,39,43] Five trials included patients with episodic migraine alone[12,15,37–39] one trial with chronic migraine alone[42] and the remaining five included patients with a combination of acute, chronic or episodic migraine, cluster, tension or benign headaches.[34–36,40,41]

Table 3D.1 summarizes patient characteristics of the 11 included studies. The total sample size was 860 (approximately 67% female) and ranged from 28 to 162 patients. Based on visual inspection of extracted data (Appendix 3D), we concluded that baseline pain scores were not substantially different between PNB and control group.

Table 3D.2 (see Appendix 3D) displays the types of medications and mode of administration for both PNB and control group. For the PNB group, seven trials studied the SPG block[12,15,34,39–42] and four trials studied the greater occipital nerve block block.[35–38] The SPG blocks were administered as intranasal droplets in five trials[12,15,34,39,41] and with the Tx360® device in two trials.[40,42] No trials studying trigger point injections met our eligibility criteria. The PNBs were administered by emergency physicians, residents, physician assistants or nurse practitioners. Five studies used lidocaine (10mg to 80mg) and six studies used bupivacaine (3mg to 80mg) as the choice of anesthetic when performing the PNB.

We classified 10 trials as placebo-controlled[12,15,34,35,37,39–42] where normal saline was used in place of local anesthetic. Two trials used standard headache treatment (e.g. dopamine antagonist) in the control arm.[36,38] Korucu et al. was included in both placebo and standard treatment comparisons, as it had two distinct control arms.[38]

3.4.2 Main Results:

All studies reported pain scores used a continuous measure according to the NRS or VAS. For the comparison of PNB versus placebo, nine studies were included in the meta-analysis. We pooled results separately at each time point (Figure 3.2). Our meta-analysis found that compared to placebo, pain scores were significantly lower in patients treated with PNBs at 1 minute, 5 minutes, 15 minutes and 30 minutes. There was low to moderate statistical heterogeneity between studies. Based on an unpublished survey of a convenience sample of 10 emergency physicians at two large academic EDs, the majority of respondents selected 15 and 30 minutes as the timepoints of most clinical importance. At 15 minutes, the pooled point estimate suggests that pain scores were significantly lower in patients treated with PNBs than placebo (MD = -1.17; 95% CI: -1.82 to -0.51, P = 0.0005) with low statistical heterogeneity between studies (I^2 = 49%, heterogeneity P = 0.07). A similar result was seen at 30 minutes (MD = -0.99; 95% CI: -1.66 to -0.32, P = 0.004) with low statistical heterogeneity between studies (I^2 = 36%, heterogeneity P = 0.18). Based on GRADE, the certainty of this evidence is moderate (due to some concerns with risk of bias).

A risk of bias summary for each included study is presented in Figure 3.3 using the Cochrane RoB tool 2.0.[31] We rated four studies as low risk of bias overall.[12,15,36,40] Four studies were rated to have some concerns due to the randomization process, deviations from the intended intervention, in the measurement of the outcome and from the selection of the reported result.[34,39,41,42] Three studies were rated as high risk of bias.[35,37,38]

We performed a sensitivity analysis for the primary outcome and excluded studies rated high risk of bias. After excluding these studies, the pooled estimates do not significantly change at 15 and 30 minutes (Appendix 3D). We also performed a sensitivity analysis for the primary outcome based on study setting and excluded studies in outpatient clinic settings to determine if

our results can be generalized to ED patients . After excluding these studies, the pooled estimates do not significantly change at 15 and 30 minutes (Appendix 3D).

For PNB versus active treatment, a meta-analysis was not possible due to an insufficient number of studies reporting outcomes at the same time points. We summarize the pain scores at the full range of observed time points within 120 mins in Appendix 3D (5, 15, 30, 45 and 60 minutes).

Six studies[12,15,35–37,40] reported adverse events. Adverse events were higher in the PNB group, which was expected due to the burning sensation caused by anesthesia. All adverse events were minor and there were no serious adverse events attributable to PNBs. The most common adverse events in the intervention arm were a burning or numbing sensation, dizziness and injection site pain. A full list of reported adverse events can be found in Appendix 3D.

Five studies reported the need for rescue medications.[12,15,36,39,40] The proportion of patients requiring rescue medications in the intervention and control arm are reported in Appendix 3D. Two studies reported the type of rescue medications as either a dopamine antagonist or IV fentanyl. The results were not consistent for this outcome.

Two studies reported any repeat visit to the ED or clinic within 72 hours due to relapse of headache[12,15] (see Table 3D.3 in Appendix 3D). Avcu et al. reported 9/66 (13.6%) repeat visits to the ED in the SPG block arm and 4/66 (6.1%) in the control arm.[15] Blanda found no patients in the SPG block arm or active therapy arm made a return visit to the ED for headache within 24 hours.[12]

3.5 Limitations

Our systematic review has some limitations. Firstly, there was significant heterogeneity for our primary outcome in terms of the time points for which pain was assessed. Multiple time points were used by studies ranging from 1 to 60 minutes. Based on a survey of local clinicians to

determine the optimal timeframe that would be considered clinically important to reassess pain, we included studies reporting pain scores within 120 minutes. There is further heterogeneity in the dosage of anesthetic and mode of administration of the PNBs, which may affect treatment success. The type of anesthetic used was either lidocaine or bupivacaine and ranged from 1.5 mg to 80 mg. Lidocaine is typically a faster acting anesthetic while bupivacaine has a slower onset of action. Second, we pooled studies comparing SPG and greater occipital nerve block together. Although these are both types of PNBs, their mechanism of action is different in terms having a different target location to block nerves responsible for pain and may contribute to heterogeneity. Despite the aforementioned heterogeneity, such as the mode of administration of PNBs in terms of differing target location, varying dosages of anesthetic and headache subtypes, we believe a meta-analysis was appropriate and allows our review to make conclusions of how ED patients with primary headaches in general may benefit from a variety of PNBs. Third, we cannot comment on the utility of trigger point injections; from the literature, physicians have had success with trigger point injections for headaches, however double-blind RCTs are rare. Fourth, three of our included studies were rated as high risk of bias overall and four studies with some concerns or unclear risk of bias. We addressed this issue by performing a sensitivity analysis and excluded studies included in the meta-analysis with high risk of bias and found no difference (Appendix 3D). Fifth, eight studies were conducted in the ED setting, while three were conducted in outpatient clinic settings. To determine if our findings can be generalized for ED patients, we conducted a sensitivity analysis (Appendix 3D) for our primary outcome and found the point estimates do not significantly change after excluding studies conducted in the clinic. Therefore, our results can be generalized for all ED patients. Blinding is a challenging issue with trials in this area since anesthesia causes a burning sensation and the associated numbness will likely unblind patients to their allocated treatment.

Lastly, establishing a clinically significant reduction in pain is important but difficult to determine. Current evidence suggests the median minimal clinically important difference (MCID) in acute pain scores for ED patients with a variety of acute pain presentations to be 1.5 (IQR 1.1 – 2.1) with a range of 0.8 to 2.4.[44] Although our pooled point estimates at 1, 2, 5, 15 and 30 minutes are less than 1.5, the confidence intervals overlap with this value and the possibility of a clinically significant improvement cannot be ruled out. Thus, we have presented some evidence to support a reduction of pain when using PNBs compared to placebo for primary headaches in the ED based on limited available data; further, the speed of onset and ease of use make PNBs more appealing than current recommended treatment options. More evidence is needed to determine if a clinically significant reduction in pain can be achieved.

3.6 Discussion

In our review, we found PNBs significantly improves pain at 1, 5, 15 and 30 minutes compared to placebo. When comparing PNBs against active therapy, there appears to be a favoured effect at earlier time points; however, we were unable to meta-analyze these studies due to limited data at similar time points. This systematic review also found PNBs are associated with minor adverse events, and there is inconclusive evidence about the need for rescue medications due to limited reporting. Duration of action is an important outcome to consider when choosing PNBs as a treatment option; however, the majority of studies examined shorter timeframes for pain. We identified only two studies[12,15] which reported repeat visits to the ED or clinic within 72 hours due to relapse of headache after treatment. While one of these studies demonstrated a higher proportion of return ED visits in the PNB group[15] (Appendix 3D), there is insufficient evidence to comment on the impact of PNBs with respect to duration of effect.

Headache presentations to the ED are complex and require thoughtful consideration by emergency physicians. Current recommendations for first line medications such as dopamine antagonists and other oral medications have several disadvantages such as slow onset to pain relief, unpleasant side effects and a less favourable route of administration. Alternatives such as PNBs have several advantages such as their relatively non-invasive route of administration and have shown promising results with their rapid time to relief. Nausea and vomiting are common symptoms with migraine and other headache presentations[45] therefore, providing oral medications is not ideal. PNBs bypass the gastrointestinal route and directly blocks the nerve bundle responsible for causing pain. This route of administration is preferred but comes with some challenges. Greater occipital nerve blocks and trigger point injections require a needle to administer a small amount of anesthetic which causes pain and anxiety for patients and carries the risk for needle stick injuries for health care professionals. The SPG block is the least invasive and safest of the three PNBs especially with intranasal drops. Furthermore, the nasal mucosa is relatively small and supplied with blood vessels allowing for rapid absorption of drugs.[46] Currently, intranasal lidocaine is listed as a weak recommendation with low quality evidence by the Canadian Headache Society,[47] and as a level C (possibly effective or ineffective for acute migraine) by the American Headache Society.[48] Our review adds evidence to support the use of SPG blocks for reducing pain within 120 minutes.

Previous systematic reviews and meta-analyses have concluded various PNBs to be effective for subtypes of headache. Chi and colleagues conducted a meta-analysis studying intranasal lidocaine and found this procedure to lower pain intensity at 5 mins (SMD = -0.61; 95% CI: -1.04; -0.19) and 15 mins (SMD = -0.72; 95% CI: -1.14; -0.19).[19] In our review, we included a broader category of the intervention and analyzed pain within 120 minutes as our primary

outcome. Dagenais and colleagues conducted a systematic review on the safety and efficacy of intranasal lidocaine for primary headaches and found this procedure to be effective from 1 minute to 30 minutes compared to placebo.[49] They however did not meta-analyze their data. Zhang and colleagues conducted a systematic review and meta-analysis on the efficacy of the greater occipital nerve block for migraine and found this procedure can significantly reduce pain intensity (MD = -1.24; 95% CI: -1.98 to -0.49; P = 0.001); however, it was not clear at what time this reduction occurred.[21] Our systematic review includes more trials than previous studies since our inclusion criteria is broad and we prespecified clinically important and meaningful outcomes. Furthermore, our review provides a summary of pain within clinically important time frames and trends that occur over time. Time to effective pain relief is an important outcome and emergency physicians require more evidence to support the use of PNBs as a first-line treatment option.

Strengths of our study is that we used a rigorous search strategy in a broad number of relevant databases which was peer reviewed by a second research librarian. Second, our review makes conclusions about pain ≤ 60 minutes, which is a clinically important time frame for emergency physicians and patients. Determining the optimal time point to reassess pain is critical for emergency physicians and depends on the source of anesthetic and other variables such as coadministration of antiemetics and other drugs. Despite the observed heterogeneity among studies with respect to the types of blocks, anesthetics and doses, the effect of PNBs on pain scores for ED patients presenting with primary headache disorders has not been summarized before. Our findings are useful for emergency physicians who may be considering the use of PNBs to treat ED patients with headache as either an adjunct or alternative to routine treatment options.

Results from our systematic review and meta-analysis have several clinical and research implications. Our findings suggest the greater occipital nerve block and the SPG block are effective

for pain relief at 1, 5, 15 and 30 minutes in the ED or clinic setting, compared to placebo. This finding is useful for emergency physicians when considering PNBs as a first-line treatment option for primary headaches. Given more evidence, this assessment may result in a faster relief of pain that is clinically significant and may have the potential to reduce IV medication and opioid use which have known side effects. This is beneficial to both patient and the healthcare system. The SPG block is the simplest and least invasive method

We found a relatively small number of relevant trials that measure clinically useful outcomes and significant heterogeneity across available studies; thus, further research is warranted to allow for more robust conclusions about whether PNBs can truly be considered as a first line alternative to other approaches. Future trials of effectiveness of PNBs should measure pain at clinically important timepoints and use standard headache therapies as the comparator. Future trials should be sufficiently powered and well designed to protect against various source of biases. More evidence is needed to compare PNBs against standard headache therapies for pain reduction within 120 minutes to determine if this procedure can be used as a first line treatment option in the emergency department and potentially reduce the use of IV medications and opioids.

Our review shows PNBs are effective as a rapid treatment option when compared to placebo; however, we were unable to assess effectiveness against standard therapy. Emergency physicians should consider PNBs as an adjunct therapy for patients with primary headache disorders.

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3.7 Tables and Figures

Figure 3.1 Flow diagram of selection process for the included studies

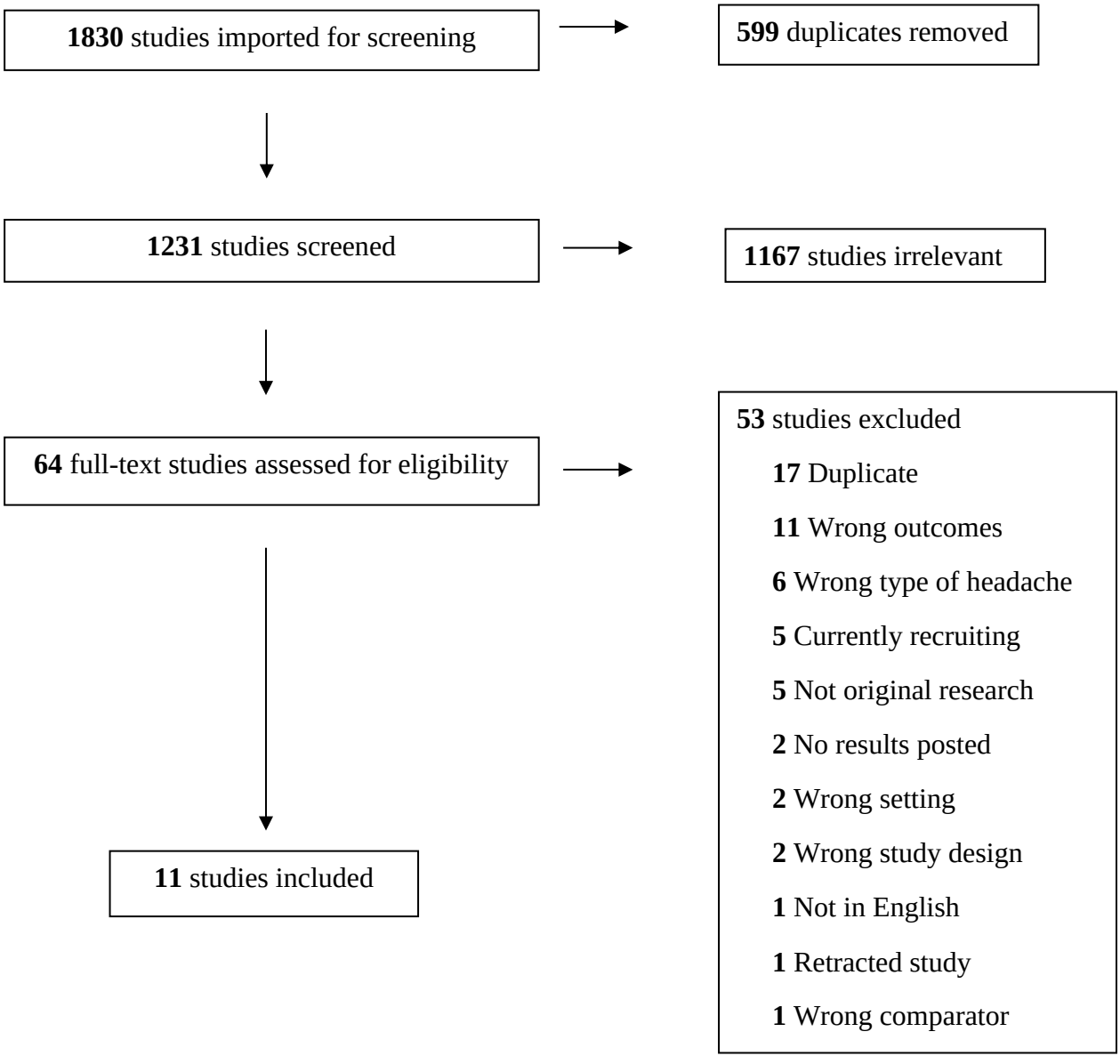
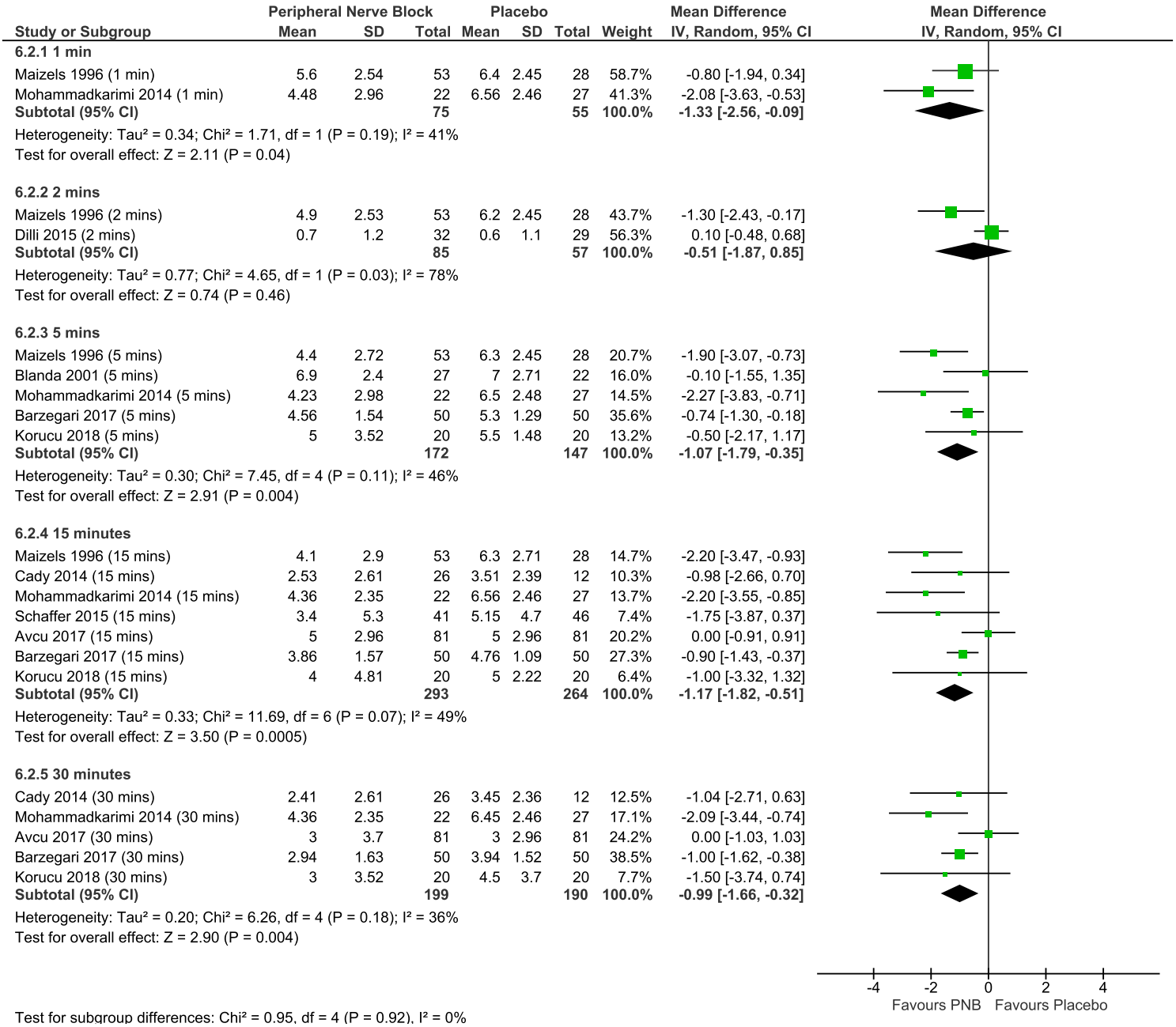


Table 3.1 Baseline characteristics of included studies

Author, Year	Country	Study Setting	Type of Primary Headache	Sample Size (N)	(% Female)	Mean age (years)	Type of Intervention	Type of Control
Maizels 1996[39]	USA	Clinic	Episodic migraine	81	67 (82.7%)	42 (36.3)	[c]SPG Block	Placebo (saline)
Blanda 2001[12]	USA	ED	Episodic migraine	49	42 (85.7%)	Not reported	SPG Block and dopamine antagonist	Placebo (saline) and dopamine antagonist
Cady 2014[43]	USA	Clinic	Chronic migraine	41	31 (75.6%)	41.3 (12.6)	SPG Block	Placebo (saline)
Mohammadkarimi 2014[41]	Iran	ED	Migraine, tension	90	Not reported[b]	Not reported[b]	SPG Block	Placebo (saline)
Dilli 2015[35]	USA	Clinic	Episodic and chronic migraine	63	55 (87.3%)	43 (14)	[d]GON Block and 0.5 mL of 20 mg methylprednisolone	Placebo (normal saline + 1% lidocaine without epinephrine)
Schaffer 2015[40]	USA	ED	Benign headache	87	64 (73.6%)	37.2 (15.95)	SPG Block	Placebo (saline)
Avcu 2017[15]	Turkey	ED	Episodic Migraine	162	125 (77.2%)	35.5 (11.3)	SPG Block and 10 mg in 100 mL of IV dopamine antagonist	Placebo (saline spray) and 10 mg in 100 mL of IV dopamine antagonist
Barzegari 2017[34]	Iran	ED	Multiple (migraine, cluster or tension)	100	54 (54%)	31.3 (8.6)	SPG Block and 7.5 mg IV dopamine antagonist	Placebo (saline 0.9% and 7.5 mg IV dopamine antagonist)
[a]Friedman 2018[37]	USA	ED	Episodic migraine	28	24 (85.7%)	37.7 (11.4)	GON Block	Sham - 0.5 mL of 0.5% bupivacaine intradermally into posterior scalp overlying the greater occipital nerve - 1 mL total
Korucu 2018[38]	Turkey	ED	Episodic migraine	60	36 (60%)	38.3 (9.2)	GON Block and 1 mL normal saline	A. Placebo (saline) B. IV dexketoprofen trometamol and 10 mg dopamine antagonist in 100 mL saline
Friedman 2020[36]	USA	ED	Episodic and chronic migraine	99	78 (78.8%)	38.5 (11)	GON Block and IV saline	Sham GON – 6 mL saline and IV dopamine antagonist

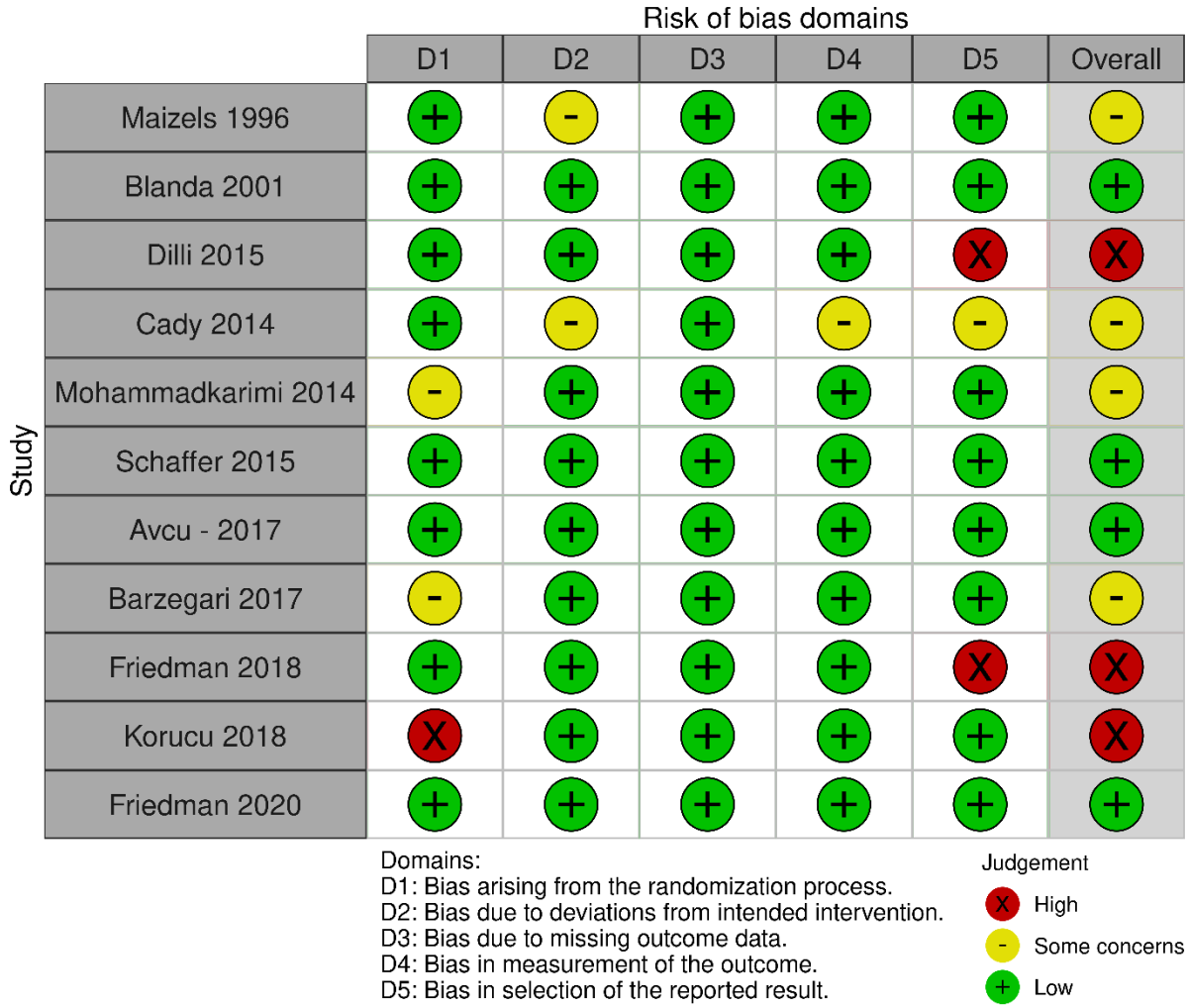
[a]Single-blind study design. All other studies were double-blinded.
[b]Age and number of female participants were not reported by migraine and tension headache subtypes. The total mean age of participants was 35.3 years (SD not reported). The mean age of patients in the intervention arm was 33.5 (13.3) years and in the control arm, 37.2 (14.6) years. There were 54 (60%) females in the intervention arm and 50 (55.6%) females in the control arm. The reported age and number of females include secondary headaches.
[c]SPG Block: Sphenopalatine Ganglion Block.
[d]GON Block: Greater Occipital Nerve Block.

Figure 3.2 Forest plot PNB vs Placebo: pain at 1, 2, 5, 15 and 30 minutes



PNB = Peripheral nerve block.
Mean (SD) were estimated from median (interquartile range) for Schaffer 2015, Avcu 2017 and Korucu 2018.

Figure 3.3 Risk of bias summary - review authors' judgements about each risk of bias item for each included study



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3.9 Appendices

3.9.1 Appendix 3A – PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6-8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix B
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7-8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-7 / Appendix C
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8-9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8

	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8-9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9

Section and Topic	Item #	Checklist item	Location of where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9, 21
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	9
Study characteristics	17	Cite each included study and present its characteristics.	9-10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	11, 24
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	10-12, 23, Appendix D
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	11. 24
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	10-11, 23
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	10, 11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11, Appendix D
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	11, 23
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	14-15
	23b	Discuss any limitations of the evidence included in the review.	12-13

	23c	Discuss any limitations of the review processes used.	12-13
	23d	Discuss implications of the results for practice, policy, and future research.	15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	1, 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1
Competing interests	26	Declare any competing interests of review authors.	1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	7, Appendix C-D

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71 For more information, visit: http://www.prisma-statement.org/

3.9.2 Appendix 3B – Search Strategy

Database: Ovid MEDLINE(R) ALL <1946 to November 23, 2020>

Search Strategy:

---

1 nerve block/ or exp autonomic nerve block/ (22181)

2 (nerve adj2 block*).tw. (13074)

3 (Ganglion Block* or nerve block*).kw. (835)

4 ((Ganglion or sphenopalatine or pterygopalatine or occipital) adj2 block*).tw,kf. (2976)

5 trigger point inject*.tw,kw. (305)

6 or/1-5 (30289)

7 exp Anesthetics, Local/ or lidocaine.tw,kf. (112130)

8 Administration, Intranasal/ or (intranasal* or intra nasal* or transnasal* or trans nasal*).tw,kf. (36933)

9 7 and 8 (643)

10 6 or 9 (30891)

11 Headache/ or exp Headache Disorders/ (59022)

12 (headache* or head ache* or migraine*).tw,kw. (105528)

13 cephalalgia*.tw,kw. (720)

14 or/11-13 (117177)

15 10 and 14 (821)

16 exp Emergency Service, Hospital/ (80736)

17 Emergency Medicine/ or Emergency Treatment/ (24210)

18 (emergenc* adj3 (department* or room* or service* or medicine or treatment)).tw. (147195)

19 (emergenc* and (department* or room* or service* or medicine or treatment)).kf. (14942)

20 Acute Disease/ (213707)

21 acute.tw,kf. (1221929)

22 randomized controlled trial.pt. (517710)

23 controlled clinical trial.pt. (93941)

24 random*.tw. (1175389)

25 placebo.ab. (212833)

26 clinical trials as topic.sh. (193727)

27 trial.ti. or groups.tw. (2294800)

28 ambulatory care facilities/ or community health centers/ or outpatient clinics, hospital/ or pain clinics/ (43151)

29 (clinic or clinics).tw,kw. (325208)

30 or/16-29 (4771741)

31 15 and 30 (307)

32 exp animals/ not humans/ (4758922)

33 31 not 32 (305)

34 limit 33 to english language (278)

Database: Embase Classic+Embase <1947 to 2020 November 23>

Search Strategy:

---

1 nerve block/ (33486)

2 exp ganglion block/ (2124)

3 (nerve adj2 block*).tw. (20054)

4 ((sphenopalatine or pterygopalatine or occipital or ganglion) adj2 block*).tw. (5075)

5 trigger point inject**.tw. (562)

6 intranasal drug administration/ and exp local anesthetic agent/ (664)

7 exp local anesthetic agent/na (391)

8 ((intranasal* or intra nasal* or transnasal* or trans nasal*) adj2 (lidocaine* or an?esth*)).tw. (176)

9 or/1-8 (45575)

10 exp *"headache and facial pain"/ (89831)

11 (headache* or migraine* or Cephalalgia*).mp. (331318)

12 10 or 11 (344208)

13 9 and 12 (2601)

14 emergency ward/ (153761)

15 emergency health service/ (103308)

16 (emergenc* adj3 (department* or room* or service* or medicine or treatment)).tw. (228646)

17 acute disease/ (105968)

18 emergency treatment/ (17817)

19 intravenous drug administration/ (393278)

20 (intravenous* or iv).ti. (163334)

21 emergency care/ (47755)

22 acute.tw. (1788311)

23 random*.tw. or placebo*.mp. or double-blind*.mp. or trial.ti. (2000158)

24 outpatient department/ (85822)

25 (clinic or clinics).tw. (555815)

26 outpatient/ (132606)

27 or/14-26 (4908926)

28 13 and 27 (1015)

29 (exp animal/ or nonhuman/) not exp human/ (7316247)

30 28 not 29 (1010)

31 limit 30 to english language (940)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <October 2020>

Search Strategy:

---

1 nerve block/ or exp autonomic nerve block/ (3854)

2 (nerve adj2 block*).tw. (6777)

3 (Ganglion Block* or nerve block*).kw. (2867)

4 ((Ganglion or sphenopalatine or pterygopalatine or occipital) adj2 block*).tw,kw. (533)

5 trigger point inject*.tw,kw. (131)

6 or/1-5 (10143)

7 exp Anesthetics, Local/ or lidocaine.tw,kw. (21433)

8 Administration, Intranasal/ or (intranasal* or intra nasal* or transnasal* or trans nasal*).tw,kw. (7552)

9 7 and 8 (254)

10 6 or 9 (10378)

11 Headache/ or exp Headache Disorders/ (5153)

12 (headache* or head ache* or migraine*).tw,kw. (27791)

13 cephalalgia*.tw,kw. (49)

14 or/11-13 (28611)

15 10 and 14 (338)

Web of Science – November 24, 2020

8

274

#6

AND

#5

Refined by: LANGUAGES: (ENGLISH)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020

7

283

#6

AND

#5

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020

Edit

6

4,367,376

TS=

(("pain clinic*")

)

OR

TS=

(trial)

OR

TS=(placebo*)

OR

TS=

(random*)

OR

TS=

(acute)

OR

TS=

(Emergency)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020

Edit

5

757

#4

AND

#3

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020

Edit

4

113,031

TS=

((migraine*)

)

OR

TS=

(headache*)

OR

TS=

(cephalalgia*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020

Edit

3

18,670

#2

OR

#1

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020

Edit

2

486

TS=

((intranasal* or intra nasal* or transnasal* or trans nasal*)

)

AND

TS=

((lidocaine OR local anesth* or local anaesth*)

)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020

Edit

1

18,233

TS=((nerve

NEAR/2

block*))

OR

TS=((((Ganglion

or

sphenopalatine

or

pterygopalatine

or

occipital)

NEAR/2

block*)))

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020

3.9.3 Appendix 3C – Data Extraction Items

Section 1: Study characteristics

1) Initials of reviewer
2) Covidence #
3) Title
4) First author (Last name, First initial)
5) Journal
6) Published Year
7) Volume, page numbers
8) Countries
9) Number of sites
10) Type of RCT
11) Study setting
12) Total Sample Size (n)
    a. Intervention group (n)
    b. Intervention mean age in year (SD) or median [median] (IQR)
    c. Intervention sex, n (% female)
    d. Control group (n)
    e. Control group mean age in year (SD) or median [median] (IQR)
    f. Control group sex, n (% female)
13) Type of Headache
14) Diagnostic Criteria (List) if Any (e.g. ICH) if none, N/A

Section 2: Medications Administered

1) Intervention Group: Mode of Administration
2) Type of Anesthetic Used
3) Concentration (%)
4) Volume (mL)
5) Amount (mg)
6) Administered By
7) Control (Medications Administered)
8) Any other comparator arms? (Y/N)
    a. If yes, what medication (s) given in this other arm? (list)
9) Notes

Section 3: Pain Intensity:

1) Pain Score Measure
2) How is Pain Reported?
3) Primary Outcome: Outcome: How many time points is pain measured at up to and including 120 mins?

4) List ALL Primary Time point(s) Measured (within 120 mins) Ex: 5min, 15min, 20min, 30min, 45min, 60min, 120min, Other()
5) Intervention Arm: Baseline Pain Score n, mean ± SD or n, [median (IQR 25%-75%)]
6) Intervention Arm: Time Point 1: _ mins Mean Pain Score, time + n, mean ± SD or n, [median (IQR 25%-75%)] (Please add a column to the right depending on # of time points measured within 120 mins)
7) Control Arm: Baseline Pain Score n, mean ± SDorn, [median (IQR 25%-75%)]
8) Control Arm: Time Point 1: _ mins Mean Pain Score, time + n, mean ± SD or n, [median (IQR 25%-75%)] (Please add a column to the right depending on # of time points measured within 120 mins)
9) Other comparator Arm: N/A if not applicable. Baseline Pain Score n, mean ± SD or n, [median (IQR 25%-75%)]
10) Other comparator Arm: N/A if not applicable Time Point 1: _ mins Mean Pain Score, time + n, mean ± SD or n, [median (IQR 25%-75%)](Please add a column to the right depending on # of time points measured within 120 mins)
11) Intervention Arm: If Pain was reported in another way such as % improvement, please extract %(%SD) or other, at time points up to and including 120 mins
12) Control Arm: If Pain was reported in another way such as % improvement, please extract %(%SD), or other at time points up to and including 120 mins
13) Other comparator Arm: N/A if not applicable. If Pain was reported in another way such as % improvement, please extract %(%SD), or other at time points up to and including 120 mins
14) Notes
15) Secondary Outcome: Is pain measured between 2 hours and 72 hours? Y/N
16) If yes, list all time points between 2 hours and 72 hours that pain is measured
17) Intervention Arm: Time Point 1: _ hours. Mean Pain Score, time + n, mean ± SD (Please add a column to the right depending on # of time points measured between 2 and 72 hours
18) Control Arm: Time Point 1: _ hours. Mean Pain Score, time + n, mean ± SD (Please add a column to the right depending on # of time points measured between 2 and 72 hours)
19) Intervention Arm: If Pain was reported in another way such as % improvement, please extract %(%SD) from 2-72 hours
20) Control Arm: If Pain was reported in another way such as % improvement, please extract %(%SD) from 2-72 hours
21) Which other secondary outcomes were reported? Please list which ones from:- Adverse events- Rescue Medications,- Re-Lapse to ED or Clinic within 72 hours. N/A if None reported
22) Were adverse effects reported in the intervention or control group?
23) Intervention Arm: How many adverse events in the intervention arm? (n) / Total N. N/A if not stated
24) Any serious adverse events related to the study treatment?
25) Which adverse events? (Please list all serious and not serious)

26) Control Arm: How many adverse events reported in the control arm? (n)/Total NN/A if not stated
27) Any serious adverse events related to the study treatment?
    a. Which adverse events? (Please list all serious and not serious)
28) Intervention Arm: How many patients in the intervention arm required rescue medications? n/N Total (%) N/A if not stated
    a. Which meds? (Please list)
29) Control Arm: How many patients in the control arm required rescue medications? n/N Total (%)N/A if not stated
    a. Which meds? (Please list)
30) How many patients in the intervention arm required re-admission to hospital or clinic within 72 hours? (n). N/A if not stated
31) How many patients in the control arm required re-admission to hospital or clinic within 72 hours?(n). N/A if not stated
32) Notes

3.9.4 Appendix 3D - Supplemental information

Table 3D.1 Journal, sites, diagnostic criteria, pain scale used and baseline pain scores of included studies

Author, Journal	Number of sites	Diagnostic Criteria Listed	Pain Scale[b]	Intervention Baseline Pain Score (mean ± SD)	Control Baseline Pain Score (mean ± SD)
Maizels, Journal of the American Medical Association[33]	Single center	International Headache Society criteria for Migraine with or without aura	NRS	7.70 ± 1.45	8.0 ± 1.55
Blanda, Academic Emergency Medicine[28]	Multi-center (2)	International Headache Society Ad Hoc Committee on Classification of Headaches	VAS	8.40 ± 1.50	8.60 ± 1.35
Cady, Journal of Headache and Pain[37]	Multi-center (2)	[1]ICHD-2	NRS	3.18 ± 2.79	3.78 ± 2.48
Mohammadkarimi, Journal of Research in Medical Sciences[35]	Single center	International Headache Society	VAS	Not reported	6.42 ± 1.82
Dilli, Cephalalgia[29]	Single center	ICHD-2	NRS	1.80 ± 2.10	1.70 ± 1.80
Schaffer, Annals of Emergency medicine[34]	Multi-center (2)	Not Specified	VAS for primary outcome and NRS for secondary	8.0 ± 2.0	7.85 ± 1.60
Avcu, Annals of emergency medicine[26]	Single center	International Headache Society Criteria for Migraine	NRS	8.0 ± 2.22	8.0 ± 2.22
Barzegari, Emergency[27]	Single center	International Headache Society and Ad Hoc Committee on Classification of Headache	VAS	6.15 ± 1.19	5.87 ± 1.01
Friedman 2018, Headache[31]	Multi-center (2)	ICHD-3	NRS	7.9 ± 1.9	7.70 ± 1.60
Korucu, Acta Neurologica Scandinavica[32]	Single center	ICHD-3	NRS	9.0 ± 1.85	[c]A. 8.0 ± 1.85 B. 8.0 ± 1.48
Friedman 2020, Headache[30]	Multi-center (2)	ICHD-3	NRS	9.0 ± 1.4	9.29 ± 1.10

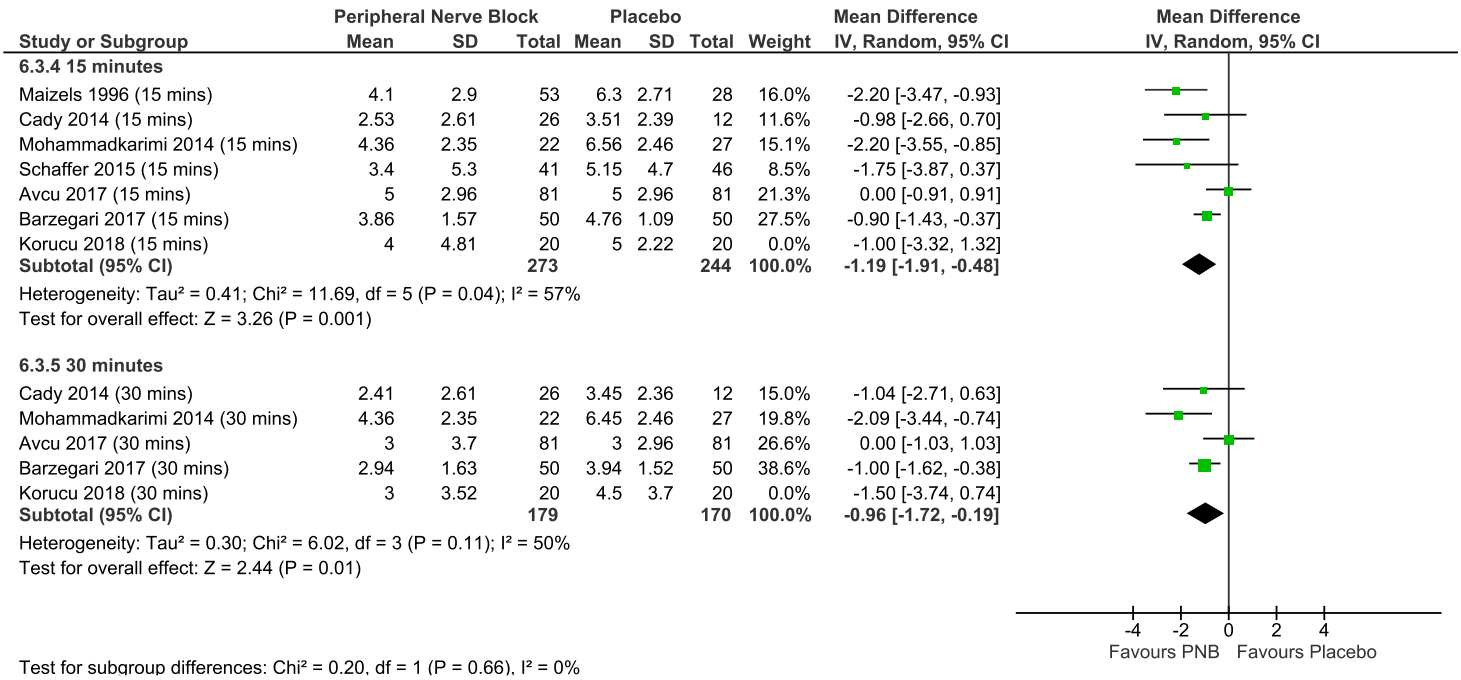
[a]ICHD: International classification of headache disorders.
[b]NRS: Numerical Rating Scale;
VAS: Verbal Rating Scale.
[c]A: Placebo (Saline)
B: IV Dexketoprofen and metoclopramide.

Table 3D.2 Intervention: Medication and mode of administration

Authors	Type of Peripheral Nerve Block Used	Type of anesthetic used	Concentration (%)	Volume (mL)	Amount (mg)	Administered by
Maizels 1996[33]	[a]SPG Block	Lidocaine	4	0.5	20	Not Stated
Blanda 2001[28]	SPG Block	Lidocaine	4	2	80	Emergency Physician
Cady 2014[37]	SPG Block	Bupivacaine	0.5	0.3	1.5	Not Stated
Mohammadkarimi 2014[35]	SPG Block	Lidocaine	10	0.1	10	Not Stated
Dilli 2015[29]	[b]GON Block	Bupivacaine	0.5	2.5	12.5	Other (Attending physician, physician assistant)
Schaffer 2015[34]	SPG Block	Bupivacaine	0.5	0.6	3	Emergency Physician
Avcu 2017[26]	SPG Block	Lidocaine	10	0.1	10	Not Stated
Barzegari 2017[27]	SPG Block	Lidocaine	2	1	20	Not Stated
[a]Friedman 2018[31]	GON Block	Bupivacaine	0.5	6	30	Other (attending emergency MD, emergency resident, physician assistants)
Korucu 2018[32]	GON Block	Bupivacaine	0.5	1	5	Not Stated
Friedman 2020[30]	GON Block	Bupivacaine	0.5	6	30	Other (attending emergency MD, emergency resident, physician assistants, nurse practitioners)

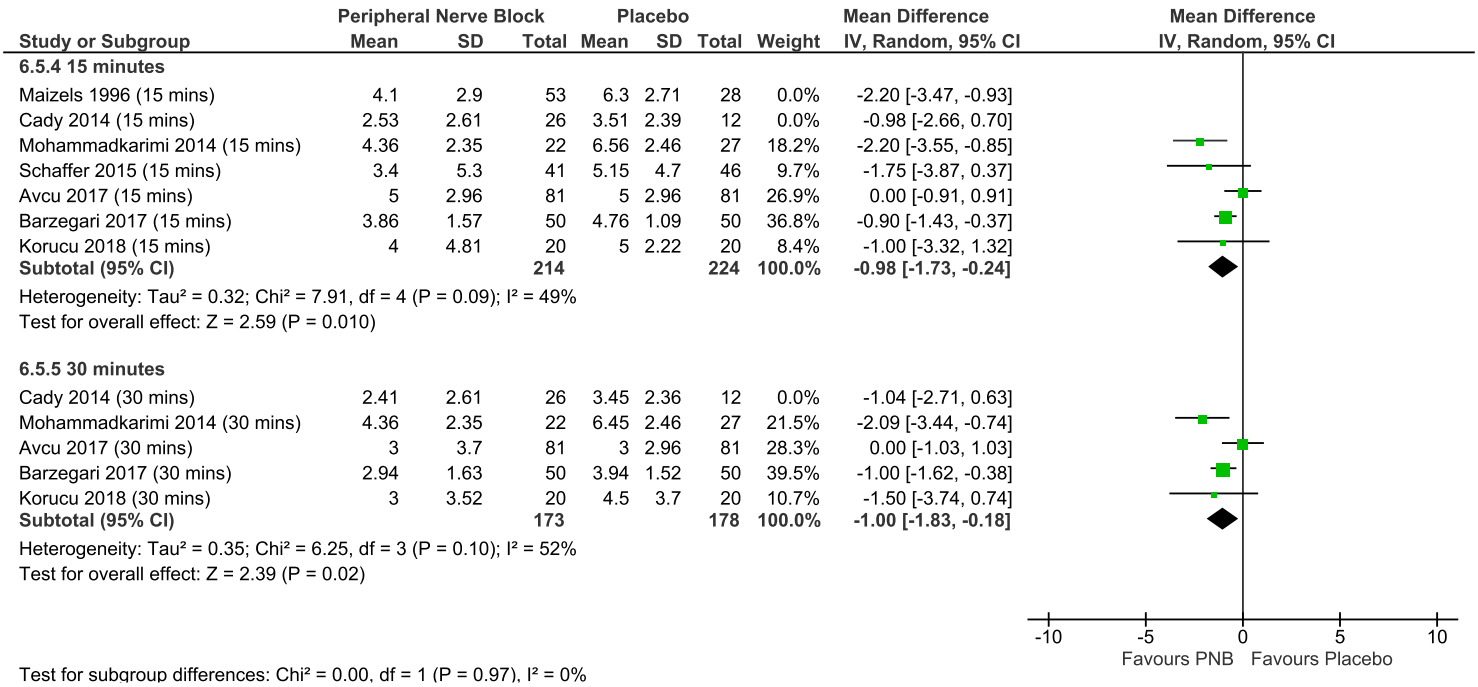
[a]SPG Block: Sphenopalatine Ganglion Block.
[b]GON Block: Greater Occipital Nerve Block.

Figure 3D.1 Sensitivity analysis of PNB vs Placebo, excluding studies at high risk of bias



PNB = Peripheral Nerve Block
Mean (SD) were estimated from median (interquartile range) for Schaffer 2015, Avcu 2017 and Korucu 2018.
Korucu 2018 was rated as high risk of bias.

Figure 3D.2 Sensitivity analysis of PNB vs Placebo in the ED setting only

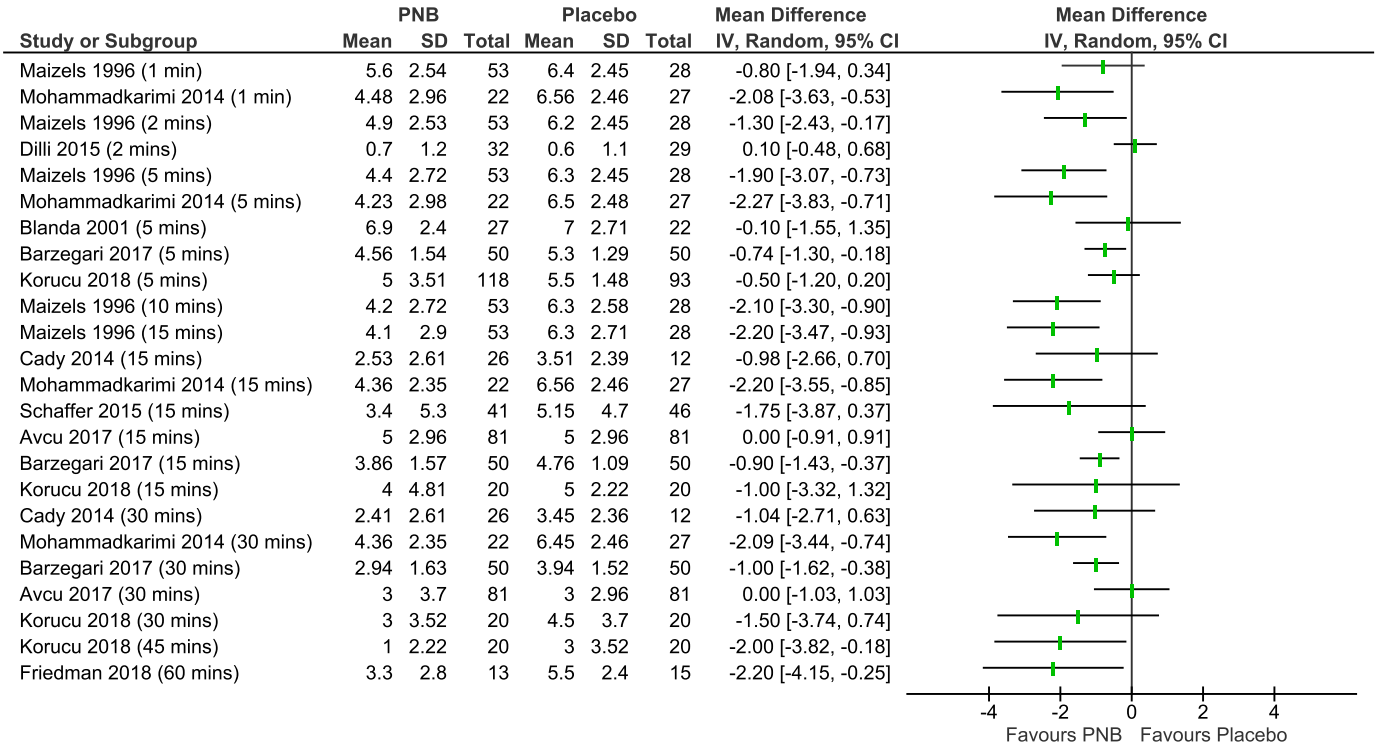


PNB = Peripheral Nerve Block

Mean (SD) were estimated from median (interquartile range) for Schaffer 2015, Avcu 2017 and Korucu 2018.

Maizels 1996 and Cady 2014 were conducted in clinic settings.

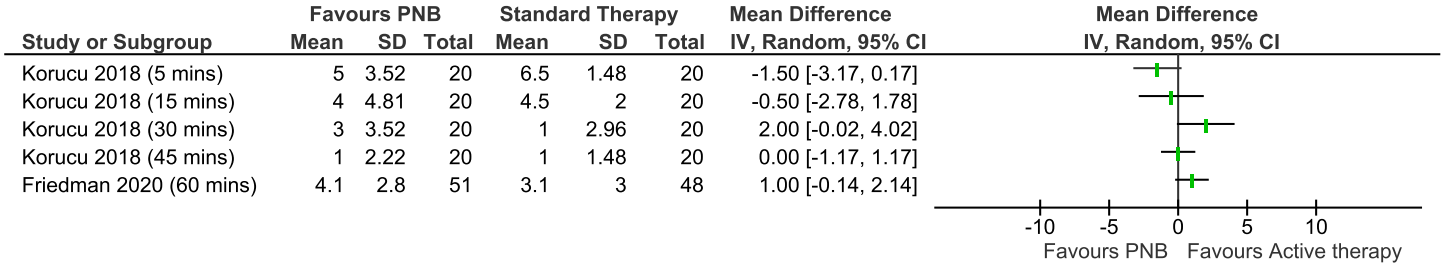
Figure 3D.3 Summary of PNB vs Placebo at various time points ≤ 60 mins



PNB = Peripheral nerve block

Mean (SD) were estimated from median (interquartile range) for Schaffer 2015, Avcu 2017 and Korucu 2018.

Figure 3D.4 Summary of PNB vs Active treatment at various time points ≤ 60 mins



PNB = Peripheral nerve block

Mean (SD) were estimated from median (interquartile range) for Korucu 2018.

Table 3D.3 Relevant secondary outcomes of included studies

	Intervention Arm			Control Arm		
Authors	**2^0: Adverse events: n/N (%), list of any events**	**2^0: Rescue medications n/N (%) – list medications used if available**	**2^0: Relapse to ED or Clinic**	**2^0: Adverse events: n/N (%), list of any events**	**2^0: Rescue medications n/N (%) – list medications used if available**	**2^0: Relapse to ED or Clinic**
Maizels 1996[33]	Number not specified - burning or numbness in the nose or in and around the eye. An unpleasant taste was often noted. Numbness in the throat was often associated with a sense of gagging	15/53 (28%) - medications not stated	N/A	Number not specified. States 'adverse events almost exclusively in intervention group'	20/28 (71%) - medications not stated	N/A
Blanda 2001[28]	6/27 (22.2%) - Akathisia (due to prochlorperazine given in both groups)	9/27 (33%) – medications not stated	0/27 (0%)	4/22 (18.2%) – Akathisia (due to prochlorperazine given in both groups)	6/22 (27%) - medications not stated	0/22 (0%)
Cady 2014[37]	Number not specified. (30 different AEs) anxiety; bad taste; blurred vision; body pain; cold; congestion; cough; diarrhea; dizziness; elevated BP; eye infection; eye sting; facial numbness, facial pain; general numbness, head pain; indigestion; lacrimation; lightheaded; mouth numbness; nasal bleeding, nasal drainage, nasal irritation; nausea; numb throat; palpitations; sinus inflammation; sinus numbness; sneeze; sore throat; tingling; tooth abscess	N/A	N/A	Number not specified. (25 different AEs) bad taste; cold; dizziness; drowsiness; ear infection; ear pain; ear ringing; eye sting; heartburn; insomnia; lacrimation; laryngitis; lightheaded; low back pain; nasal bleeding; nasal irritation; nasal swelling; neck pain; occipital pain; palpitations; pneumonia; sinus infection; sore throat; sprained ankle, thumb laceration	N/A	N/A
Mohammadkarimi 2014[35]	N/A	N/A	N/A	N/A	N/A	N/A
Dilli 2015[29]	7/33 (21%) - Injection site pain, abdominal distention,	N/A	N/A	8/32 (22%) - Injection site pain, Benign intracranial	N/A	N/A

	fat redistribution, injection site paresthesia, neuralgia, weight increased			hypertension, fatigue, hypoaesthesia, lymphadenopathy, myalgia, nausea, pain (unspecified), pain of skin (scalp tenderness)		
Schaffer 2015[34]	5/36 (13.9%) - Nasal dryness, runny nose, sore throat before going to bed, congestion pre and post, hoarseness	23/41 (56.1%) – dopamine antagonist (prochlorperazine; metoclopramide)	N/A	3/40 (7.5%) - Slight nosebleed, slight runny nose, minor bloody nose in the morning	29/46 (63%) – dopamine antagonist (prochlorperazine; metoclopramide)	N/A
Avcu 2017[26]	41/81 (50.6%) - palpitations (sinus tachycardia); local irritation	10/81 (12.3%) - intravenous fentanyl	9/66 (13.6%)	9/81 (11.1%) - Transient irritation in the application area (nose)	14/81 (17.3%) - intravenous fentanyl	4/66 (6.1%)
Barzegari 2017[27]	0 (0%)	N/A	N/A	0 (0%)	N/A	N/A
[a]Friedman 2018[31]	4/13 (30.8%) - Injection site pain, neck pain, shingles	N/A	N/A	2/15 (13.3%) - Neck pain; dizziness	N/A	N/A
Korucu 2018[32]	0 (0%)	N/A	N/A	0 (0%)	N/A	N/A
Friedman 2020[30]	16/51 (31%) - dizziness, worsening or changed headache, head numbness, injection site reaction, GI symptoms	17/51 (33%) – medications not stated	N/A	18/48 (38%) - dizziness, drowsiness, worsening or changed headache, injection site reaction	8/48 (17%) - medications not stated	N/A

Chapter 4: Current Practice for Primary Headache Disorders and Perspectives on Peripheral Nerve Blocks Among Emergency Physicians in Canada: A National Survey

Authors:
*Dilan Patel[1,2], BSc
Monica Taljaard[1,2], PhD
Krishan Yadav[2,4], MD, MSc
Daniel James[3,4], MD
Jeffrey J. Perry[1,2, 4], MD, MSc

Author Affiliations:
1. School of Epidemiology and Public Health, University of Ottawa, K1G 5Z3 Ottawa, Ontario, Canada.
2. Clinical Epidemiology Program, Ottawa Hospital Research Institute, ON K1Y 4E9 Ottawa, Ontario, Canada
3. Department of Anesthesia and Pain Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada
4. Department of Emergency Medicine, University of Ottawa, Ontario, Canada

*Corresponding Author
Dilan Patel
Clinical Epidemiology Program, Department of Emergency Medicine
Ottawa Hospital Research Institute

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Author Contributions:

This manuscript was conceptualized by DP, MT, KY and JJP. Data collection and research coordination was carried out by DP. Statistical analysis was conducted by DP and MT. This manuscript was supervised by JJP and MT. The original draft was written by DP. The writing, reviewing, and editing of this manuscript was conducted by DP, MT, KY, DJ and JJP.

4.1 Abstract

Objectives:

The treatment of primary headache disorders in the emergency department (ED) is variable. This national postal survey aimed to examine Canadian emergency physicians' practice patterns with respect to drug treatment and perspectives on the use of peripheral nerve blocks (PNBs).

Methods:

We surveyed 500 emergency physicians listed in the Canadian Medical Directory according to a modified Dillman's method: an initial invitation was followed by up to four reminders to non-responders. Physicians were asked 12 questions regarding their demographics and practice setting, frequency of medication administration and perspectives towards PNBs.

Results:

Of 500 mailed surveys, 468 were delivered and 179 physicians responded (response rate 38.2%). The majority of physicians were male (63.9%); 80.6 % had been in practice for ≥10 years with 50.7% in a community or district general teaching hospital. Commonly used pharmacotherapies for primary headaches were intravenous (IV) dopamine antagonists (69%), co-administration of ketorolac and a dopamine antagonist (54.2%), IV fluid boluses (54%), non-steroidal anti-inflammatory drugs (NSAIDs) alone (53.5%), and acetaminophen (51.4%). Only 80 of 144 physicians (55.6%) reported previous experience with PNBs (95% CI: 0.48 to 0.65). The sphenopalatine ganglion block was used the least frequently. The majority (85.0%) agreed PNBs are safe and 55.1% agreed they are effective. The vast majority (84.3%) would consider PNBs as a first-line treatment option given sufficient evidence from a future trial (95% CI: 0.78 to 0.90).

Conclusion:

IV NSAIDs alone, as well as dopamine antagonists with or without ketorolac are commonly used for primary headache in Canadian EDs. Importantly, a large proportion of physicians have never used a PNB in their practice. Among those who have experience with PNBs, the majority find them safe and effective. The majority of respondents would consider PNBs as a first-line treatment option given sufficient evidence from a future trial.

4.2 Introduction

Headaches are a common neurological problem which can be disabling and negatively impact quality of life. The most common headache disorders are primary headaches, including tension-type headache, migraine, and trigeminal autonomic cephalalgias (such as cluster headache) with a global prevalence of 10%, 40% and 0.1% respectively.[1] According to the Global Burden of Disease, migraine alone was the sixth highest cause worldwide of years lost to a disability, and headaches collectively ranked third.[2,3] Benign headaches account for 1-4% of emergency department (ED) visits per year.[4–8] In the context of emergency medicine, the treatment of benign headaches include a diverse range of first-line pharmacotherapies.[9] Although these treatment options are effective, they may be considered suboptimal in an ED setting due to untimely effective pain relief, unfavourable route of administration, and rare but severe side effects.[10–14] Those who are treated ineffectively for headache disorders may be at increased risk of developing more severe and chronic forms of headache or may relapse into recurrent migraine or headache post initial treatment thus resulting in repeat ED visits.[15]

Peripheral Nerve Blocks (PNBs) including the occipital nerve block, sphenopalatine ganglion (SPG) block and trigger point injections are minor bedside procedures which involve administration of a small volume of a local anesthetic agent to promote neural blockade and break the pain cycle.[16] Based on current evidence, PNBs are effective compared to placebo at 1, 5, 15 and 30 minutes for primary headaches and should be considered as an adjunct therapy; however, there is insufficient evidence to determine if PNBs can be used as a first line alternative.[17] PNBs are currently understudied and the Canadian Headache Society only provides a weak recommendation for their use due to insufficient evidence.[18] The frequency of use and emergency physician attitudes toward use of PNBs across Canada is currently unknown.

We conducted a postal survey of emergency physicians across Canada and our primary objective was to determine the current frequency of use of drug therapies and PNBs for primary headache disorders among emergency physicians. Additional objectives were to determine attitudes and perspectives on PNBs including i) safety and effectiveness, measured on a trinary scale ("agree", "disagree", "I have not done enough PNBs to answer"), ii) comfort level, measured on a 5-point Likert scale ("very comfortable", "comfortable", uncomfortable", "very uncomfortable" or "N/A I have not done enough PNBs to answer"), iii) whether their patients have experienced a significant reduction in pain from PNBs, and iv) whether or not PNBs would be considered as a first line treatment option. We also measured emergency physicians' perceptions about a future planned randomized controlled trial studying the SPG block for primary headaches compared to standard treatment, including i) preferred route of administration for an SPG block ii) the most clinically meaningful time to reassess patient's benign headache pain, and iii) likelihood of enrolling their benign headache patients into such a study. Responses were measured categorically.

4.3 Methods

4.3.1 Study Design and Setting

We administered a national postal survey to a simple random sample of 500 Canadian emergency physicians listed in the Scott's Canadian Medical Directory, 2019 edition.[19] The Canadian Medical Directory provides a list of 99% of all practicing physicians in Canada. We randomly sampled 500 emergency physicians from the 2,955 physicians listed in this edition. The random sample was selected by applying computer-generated random numbers to sort the physicians in random sequence and selecting the first 500 eligible names. We excluded physicians

who were not treating adults in emergency medicine at the time of answering the survey. This study was coordinated by the Clinical Epidemiology Program at The Ottawa Hospital Research Institute between June 2021 and December 2021.

4.3.2 Survey Design and Content

We designed the survey based on a modified Dillman's Tailored Design for questionnaires.[20] The questionnaire was developed in collaboration with experienced emergency physicians with content expertise in pain medicine and neurology, as well as an experienced statistician. It was divided into three sections: (1) Current practice for benign headaches specific to drug therapies; (2) Perspectives on peripheral nerve blocks; and (3) Physician demographic and practice setting. Response scales were binary options (yes, no), 5-point Likert (always, most of the time, some of the time, almost never, or never) and other questions. Some questions were open ended and required a written response.

Prior to finalizing our questionnaire, we performed cognitive interviews in English and French with 10 attending emergency physicians or resident physicians at The Ottawa Hospital. Cognitive interviews involve observing respondents complete a survey and identify any issues as they read the questions aloud, such as wording, grammar, re-wording, or re-ordering of questions as appropriate to provide overall content validity. The interviewer assessed facial expressions, asked probing questions if the respondent appeared confused or had negative emotion, and gathered comments; each iteration was modified until a finalized survey was procured (see Appendix 4F). The cognitive interviews were conducted virtually over Microsoft Teams (Redmond, Washington, United States). After the English survey was finalized, the survey was translated in French by an official translator at the Ottawa Hospital Research Institute. The final survey was two pages and consisted of 12 questions which could be completed in approximately

10 minutes. The protocol, survey and all supporting documents were approved by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) (Appendix 4A – 4H).

4.3.3 Survey Administration

We pilot tested the finalized survey questionnaire on 20 emergency physicians across Ontario and Quebec to identify any challenges in our mailing procedure. After receiving three completed surveys from the initial pilot mailout with no issues, we mailed the remaining questionnaires (n = 480). Initial letters included a cover letter and questionnaire, an information sheet, a postage-paid return envelope and a $5 Tim Horton's™ coffee card. Returned surveys were addressed to the coordinator center mailroom located at The Ottawa Hospital. Reminders were sent every three weeks; envelopes contained a reminder letter, a new copy of the questionnaire, an information sheet and a postage-paid return envelope. A total of four reminders were sent to non-responders. The fourth and final reminder was delivered using Canada Post Xpresspost™, a special contact method which is larger, more visually appealing, with a tracking number to ensure receipt of delivery and guarantees shipping between 1-3 business days. Dillman's method recommends a pre-notification letter prior to sending the initial survey, however a previous study found the inclusion of a pre-notification letter resulted in a 16.5% lower response rate compared to those who did not receive a pre-notification letter, therefore we omitted this step.[20,21] As an a priori embedded study, to be reported in Chapter 5, we randomly assigned half (n = 250) of the physicians to receive electronically signed recruitment letters or reminder letters and the other half (n = 250) to receive hand signed recruitment letters or reminder letters. This was done to determine if the type of signature had any effect on the response rate. For letters that were returned to sender due to unknown or outdated address, we searched the appropriate provincial regulatory body's website

(e.g. Ontario College of Physicians and Surgeons) to determine if there was a change in location and attempted to resend the survey to their primary practice location.

4.3.4 Sample size rationale

A sample of 500 emergency physicians with an anticipated response rate of 50% was considered adequate to estimate prevalence using a two-sided 95% confidence interval with a margin of error no greater than 6.2% assuming the most conservative prevalence estimate of 0.5.

4.3.4 Data analysis:

Data were manually entered into Microsoft Excel (Redmond, Washington, United States). Differences between respondents and non-respondents were assessed using chi-squared tests. We also compared overall physician gender and age in our survey to known distributions in the emergency medicine profile of the Canadian Medical Association. We used descriptive statistics (frequency and percentage) and bar charts to summarize emergency physicians' responses. Prevalence of use of each type of drug therapy was described by collapsing "always" or "most of the time" and comparing with "some of the time", "almost never" or "never" (as "high" and "low" respectively). Two-sided 95% confidence intervals (CIs) were calculated around the main outcomes. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

4.4 Results

4.4.1 Response Rate

A total of 500 questionnaires were mailed; 32 questionnaires were returned to sender and undeliverable. After attempting to re-send questionnaires where an updated primary practice location was available, our final eligible sample size was 469. Of the 469 delivered questionnaires,

we received 174 completed questionnaires for a response rate of 37.1%. Among these, 35 respondents indicated they were currently not treating adults in emergency medicine; thus, 144 respondents were eligible and included in our analysis (Figure 4.1).

4.4.2 Physician Demographics and Practice Setting

Table 4.1 displays physician demographics and practice setting of the eligible respondents. The majority (63.9%) of emergency physicians were male and practicing in Ontario (38.9%) or Western Canada (31.3%). The majority of respondents had been practicing emergency medicine for 10 or more years (80.6%) and most physicians held a Canadian College of Family Physicians with a specialization in emergency medicine (CCFP-EM) professional designation (56.1%). The vast majority (50.7%) practiced in a community or district general teaching hospital which accounts for ≥ 60,000 ED visits per year (57.0%). Surveys were administered in French to 19.4% of respondents who were primarily francophone.

4.4.3 Current Practice for Primary Headaches: Pharmacotherapies

Figure 4.2 display the frequency of various pharmacotherapies used for primary headaches in Canadian EDs among 140 emergency physicians, arranged from most to least frequent. Responses are reported in their raw format in Appendix B. Medications which are used with high frequency for primary headaches include IV dopamine antagonists (69%), oxygen therapy for cluster headaches (57.9%) co-administration of ketorolac and a dopamine antagonist (54.2%), IV NSAIDs (e.g. ketorolac) (53.5%), IV fluid boluses ≥ 500 mL (54%) and acetaminophen (51.4%). Opioids and other serious and potentially harmful medications including IV propofol and IV ketamine have a very low frequency of use and only parenteral opioid were reported to be used "always" or "most of the time" by two (1.7%) respondents.

4.4.4 Peripheral Nerve Block Use among Canadian Emergency Physicians

Figure 4.3 displays the frequency of use of PNB use among Canadian emergency physicians, as a percentage of frequency for each type of PNB. A total of 80 (56.3%) report having performed a PNB before (95% CI: 0.48% to 0.65%). Among this proportion, the occipital nerve block is the most commonly used form of PNB for primary headaches compared to the SPG block or trigger point injections. A total of 34 (43%) of physicians report they have performed this procedure ≥ 20 times in their practice while only 6 (9.5%) and 12 (17.4%) have performed an SPG block or trigger point injections ≥ 20 times, respectively.

4.4.5 Perspectives and Attitudes Towards Peripheral Nerve Blocks

Table 4.2 presents the perspectives and attitudes towards PNBs amongst 80 emergency physicians who reported having previous experience with these procedures. The majority agree that PNBs are effective (55.1%) and safe (85.0%); 54.9% would not consider using a PNB for migraines or cluster headache (84.8%); 36.3% would consider using an occipital nerve block or trigger point injection (30%) for tension headache. The majority of emergency physicians report PNBs as comfortable to use (54.2%) and 77.5% report their patients have experienced a significant reduction in pain after administration of a PNB.

4.4.6 Design Features of a Future Trial

Table 4.3 displays emergency physician perspectives on design features of a future trial studying the SPG block for primary headache disorders. Given sufficient evidence from a randomized controlled trial, 84.3% of all emergency physicians surveyed would consider giving a PNB as a first line treatment option (95% CI: 0.78 to 0.90). Most physicians are unsure of their preferred mode of administration (60.2%); however, 17% of respondents stating a preferred route, would opt for intranasal droplets (16.8%) or cotton tip applicators (15.9%). The majority of physicians (54.1%) support 60 minutes as the most clinically significant time to reassess pain, post

treatment, and 58.8% of respondents agree with a 3 or 4-point reduction in pain on a 10-point scale as a clinically significant improvement compared to baseline pain. The majority of physicians (69.6%) would consider enrolling their patients with benign headache into a future trial comparing the SPG block against standard of care.

4.4.7 Characteristics of Respondents and Non-Respondents

Table 4.4 compares characteristics of respondents (N=179) and nonrespondents (N=289) based on geographical region and language preference. There was no significant difference between responders and non-responders with respect to geographical region (P = 0.53) but a higher proportion of respondents were French-speaking (47.8%) compared to English-speaking (36.7%) (absolute difference, 11.1%, 95% CI: -1.75% to 24%, P=0.084). The percentage of physicians who were male (63.9%) were similar to those listed in the emergency medicine profile of the Canadian Medical Association (69%); furthermore, based on years of practice, 80.6% of our respondents were approximately over the age of 40, compared to 76% of those in the Canadian Medical Association listed as age 35 to 64.[22]

4.5 Discussion

4.5.1 Summary of Main Findings

This survey reports current practice patterns of pharmacotherapies and perspectives of PNBs for primary headache disorders among emergency physicians in Canada. We found that the majority of physicians will use IV dopamine antagonists, IV NSAIDs, oral acetaminophen and a combination therapy containing consisting of ketorolac and dopamine antagonists, as the main pharmacotherapies for benign headaches in the ED. As suspected, the frequency of use of opioids and other sedatives (i.e. propofol and ketamine) was low, with the majority of physicians

prescribing them almost never or never. This shows current ED physicians comply with recommendations and guidelines from the Canadian Headache Society.[18,23,24] A large proportion of emergency physicians reported having never performed a PNB and the least commonly used procedure was the SPG block. Importantly, the majority of physicians would consider PNBs as a first-line treatment option given sufficient evidence from a RCT.

4.5.2 Prior Studies

To the best of our knowledge, this is the first national survey to identify emergency physician perspectives and attitudes towards the use of PNBs for the treatment of primary headache disorders. The optimal treatment of primary headache disorders in the ED remains an important area of research due to the suboptimal profile of recommended pharmacological treatment options. Multiple RCTs have been conducted studying the effects of various PNBs for the treatment of various primary headache disorders; however there is significant heterogeneity and meta-analyzing pain scores at similar timepoints when comparing PNBs to standard treatment is not possible.[17]

Our survey suggests a large proportion of emergency physicians have never performed a PNB; however, would consider one as a first-line treatment option given sufficient evidence from an RCT. This finding is consistent with a recent observational study where the treatment of primary headaches in the ED with PNBs were used in only 10 of 553 (1.8%) cases.[25] The greater occipital nerve block is the most commonly used technique whereas the SPG block is the least commonly performed and suggests occipital nerve blocks may be more commonly known amongst experienced emergency physicians.

An important consideration for physicians with treatment of headache pain is a clinically significant improvement for safe discharge home. Often, numerical or visual rating scales are used

to assess pain at baseline and post-treatment. From our survey, physicians report a 3- or 4-point reduction in pain on a 10-point scale as clinically significant. This contradicts with an existing systematic review which found a reduction of 1.5 points (IQR: 1.1-2.1) as the absolute minimum clinically important difference for mixed patients in the ED for pain relief.[26] While a 3 or 4 point reduction in pain may not be possible based on current evidence which shows PNBs as improving pain by approximately 1 point at 15 and 30 minutes, pain relief is subjective and PNBs may accelerate pain relief while minimizing the need for pharmacotherapies which have known side effects.[17] Improvement in pain scales should not be the only metric for discharging patients home since this is subjective and will vary from patient to patient. Other useful measures are complete pain relief, overall patient satisfaction, side effect resolution or assessments on functional scales to assess mobility of other functions.

4.5.3 Strengths and Limitations

Our study has several strengths. Our survey was designed following a modified Dillman's Tailored Design technique.[20] We conducted cognitive interviews virtually over Microsoft Teams (Redmond, Washington, United States), piloted our survey, and used four reminders to increase our response rate.

Our study has several limitations. We obtained a relatively modest response rate of 38.1%. A major concern with low response rates is non-response bias due to characteristics of non-responders being different than those of responders in ways that could be associated with the outcomes of interest, or physicians who do not like PNBs may choose to not respond to our survey. However, we have no reason to believe that physicians who chose not to respond would have responded systematically different than those who chose to respond. Additionally, the physician demographics in our survey are similar to those listed in the emergency medicine profile of the

Canadian Medical Association, including gender and age, which supports the generalizability of our results. Although, a higher-than-expected proportion of respondents were francophone, we have no reason to believe that practice patterns differ based on language the survey were administered in. Several factors might explain the relatively low response rate. The COVID-19 pandemic has been known to cause increased stress on Canadian EDs and may have resulted in physicians not having time to complete postal surveys. Furthermore, response rates from surveys of health care providers have been declining with time.[27,28] We used rigorous methodologies in our postal survey and anticipated a 50% response rate based on previous surveys using similar methods.[29,30] Postal surveys typically have a higher response rate compared to electronic surveys; recent surveys among emergency physicians using email have response rates of less than 35%.[31–33] Regarding emergency physician demographics, most physicians had been in practice for 10 or more years; however, this population may be less likely to perform newer or different techniques such as PNBs. Most physicians practiced in an academic health centre or community teaching general hospital; thus, physicians in rural or non-teaching hospital settings are under-represented.

4.5.4 Clinical Implications

Our study has several clinical implications and considerations for the future of primary headache management in the ED. The majority of emergency physicians vary their pharmacological management according to the type of primary headache a patient may have; thus, migraines are treated differently compared to tension or cluster headaches. When emergency physicians were asked which type of PNB they would prefer for each type of headache, the majority would consider the occipital nerve block or trigger point injection for tension headaches, and less than half would consider a PNB for migraine headaches; physicians typically would not consider a PNB for cluster headaches. Migraine headaches are the most prevalent form of primary

headache presentation to the ED, thus most trials recruit patients with only migraine[17]; however PNBs may be effective for acute headache pain in general. For example, the SPG is a large extracranial parasympathetic ganglion which plays a vital role in controlling pain stimuli, or nociception, of the head and face region, due to its association with the trigeminal nerve. Since primary headache disorders are associated with parasympathetic activation, blocking the SPG is a viable option for all headache pain including migraine, tension and cluster headaches.[13,34] There may be some uncertainty amongst emergency physicians as to which PNB to use for specific subtypes of headache; the majority of physicians would not consider a PNB for migraine. If PNBs are more effective than standard treatment options, they may be used on any primary headache presentations without the need to vary or alter pharmacotherapies with known side effects.

The choice of initial treatment is important for emergency physicians. Currently, NSAIDs and dopamine antagonists are recommended as first-line treatment options and may be associated with a decreased need for rescue medication.[35] Given the suboptimal profile of these pharmacotherapies, PNBs may be a viable first-line alternative.

4.5.5 Research Implications

The SPG block is perhaps the simplest and least invasive form of PNB where intranasal droplets of lidocaine may be administered to block the SPG intranasally and alleviate headache pain. A future trial is needed to study the SPG block compared to a combination of dopamine antagonists and NSAIDs to determine their comparative effectiveness. Most physicians would consider enrolling patients into such a trial; the physicians who were uncertain stated the main barrier was time and difficulty in managing this study in a busy ED setting. With sufficient training, the SPG block can be shown to be a quick and easy method especially using techniques such as the Method of Barre, where the patient lies in a supine position with their head hanging from the

edge of the bed, with their head turned 30^{o} to the side with the headache and administering droplets of lidocaine intranasally.[36–38] The results from our survey can be used to inform several important aspects of a future trial. Most physicians are unsure of their preferred mode of administration for an SPG block, likely due to minimal experience; however, we suggest the Method of Barre, or intranasal droplets as the simplest method. A future trial should reassess pain at 30 and 60 as the primary outcome, measured on a 10-point pain scale. Most physicians believe a clinically significant improvement in pain from baseline is 3 or 4 points; while this level of improvement may not be possible based on current evidence where pain was improved by approximately 1 point at 15 minutes and 30 minutes compared to placebo, improvement is subjective and will vary from patient to patient. Therefore, improvement in pain scales should not be the only metric for discharging patients with benign headaches home from the ED.

4.6 Conclusions

IV NSAIDs alone, as well as dopamine antagonists with or without ketorolac are commonly used pharmacotherapies for primary headache disorders in Canadian EDs. Importantly, a large proportion of physicians have never used a PNB in their practice. Among those who have experience with PNBs, the majority find them safe and effective. The vast majority of respondents would consider PNBs as a first-line treatment option given sufficient evidence from a future trial.

4.7 Tables and Figures

Figure 4.1 Participants and Response Rate

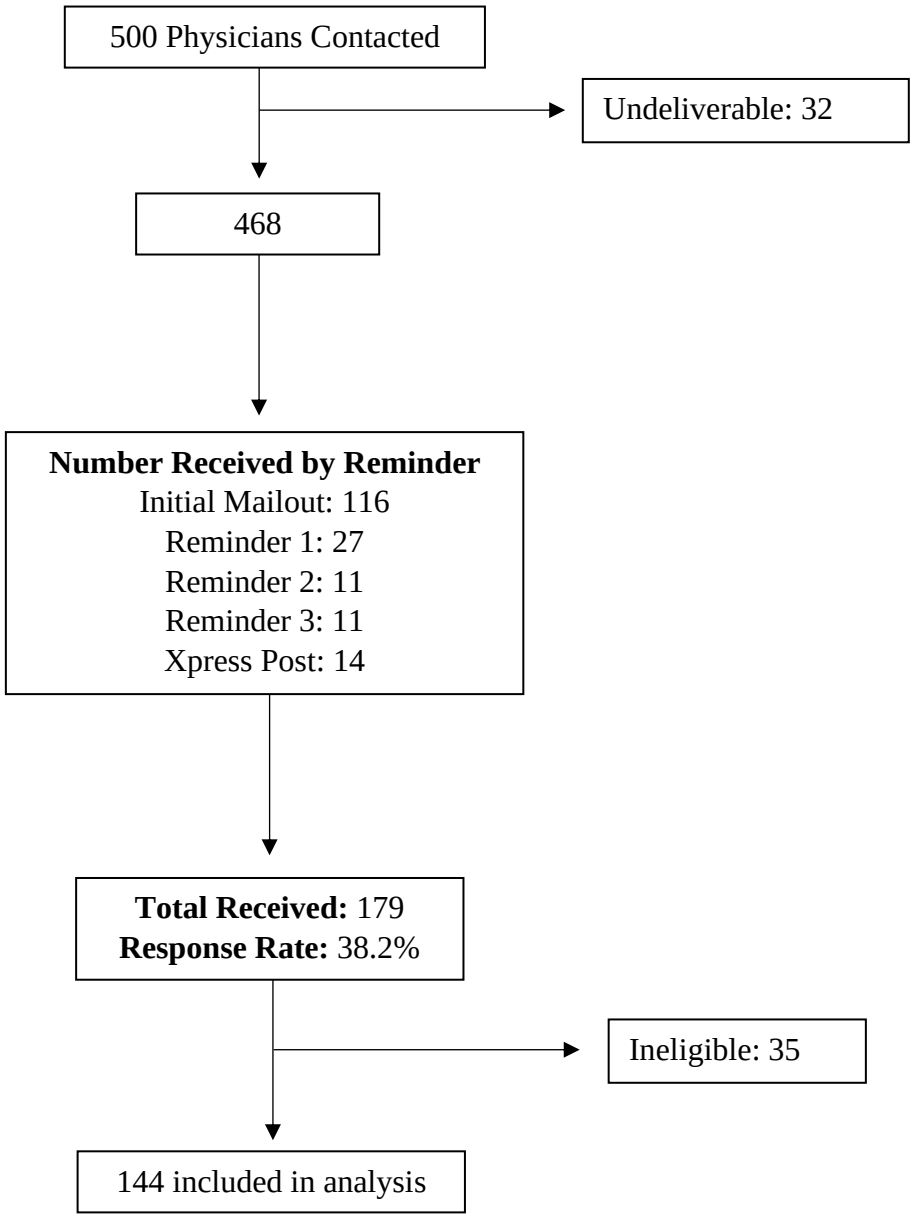


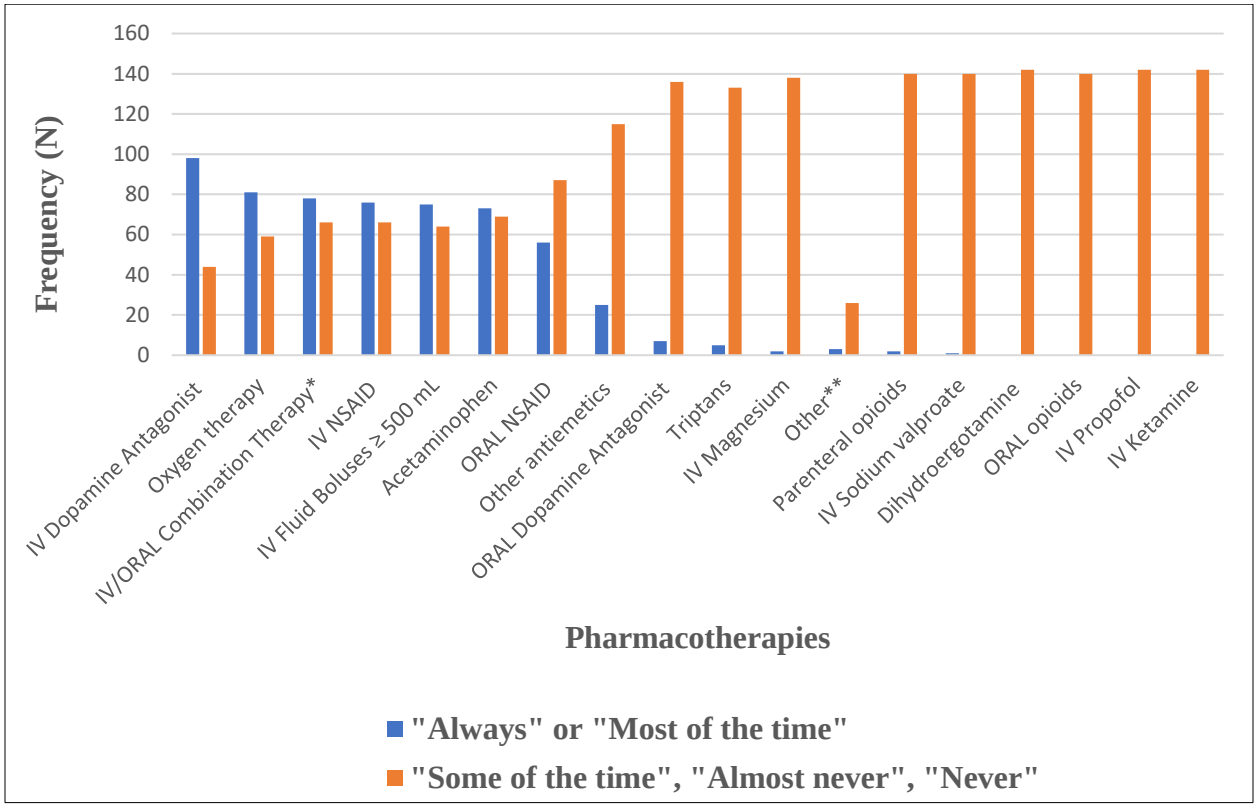
Table 4.1 Emergency Physician Demographics and Practice Setting (N=144)

Characteristics	Total Respondents N (%)
Gender	
Male	92 (63.9)
Female	51 (35.4)
Other	0 (0)
Prefer not to say	1 (0.7)
Language	
English	116 (80.6)
French	28 (19.4)
Region*	
Ontario	56 (38.9)
Western Canada	45 (31.3)
Quebec	31 (21.5)
Eastern Canada	12 (8.3)
Years of practice	
1-4	5 (3.5)
5-9	23 (16.0)
10-19	58 (40.3)
≥ 20	58 (40.3)
Canadian professional designation**	
CCFP-EM	97 (56.1)
FRCPC-EM	40 (23.1)
CCFP	28 (16.2)
Other	8 (4.6)
Practice setting	
Academic Health Centre	44 (29.7)
Community/District General Hospital: Teaching	75 (50.7)
Community/District General Hospital: Non-Teaching	18 (12.2)
Rural	9 (6.1)
Other	2 (1.4)
Patient visits to ED per year	
< 30,000	19 (13.4)
30,000 – 59,999	42 (29.6)
60,000 – 79,999	44 (31.0)
> 80,000	37 (26.0)

*Western Canada: British Columbia, Alberta, Saskatchewan, Manitoba
Eastern Canada: New Brunswick, Nova Scotia, Newfoundland and Labrador, Prince Edward Island

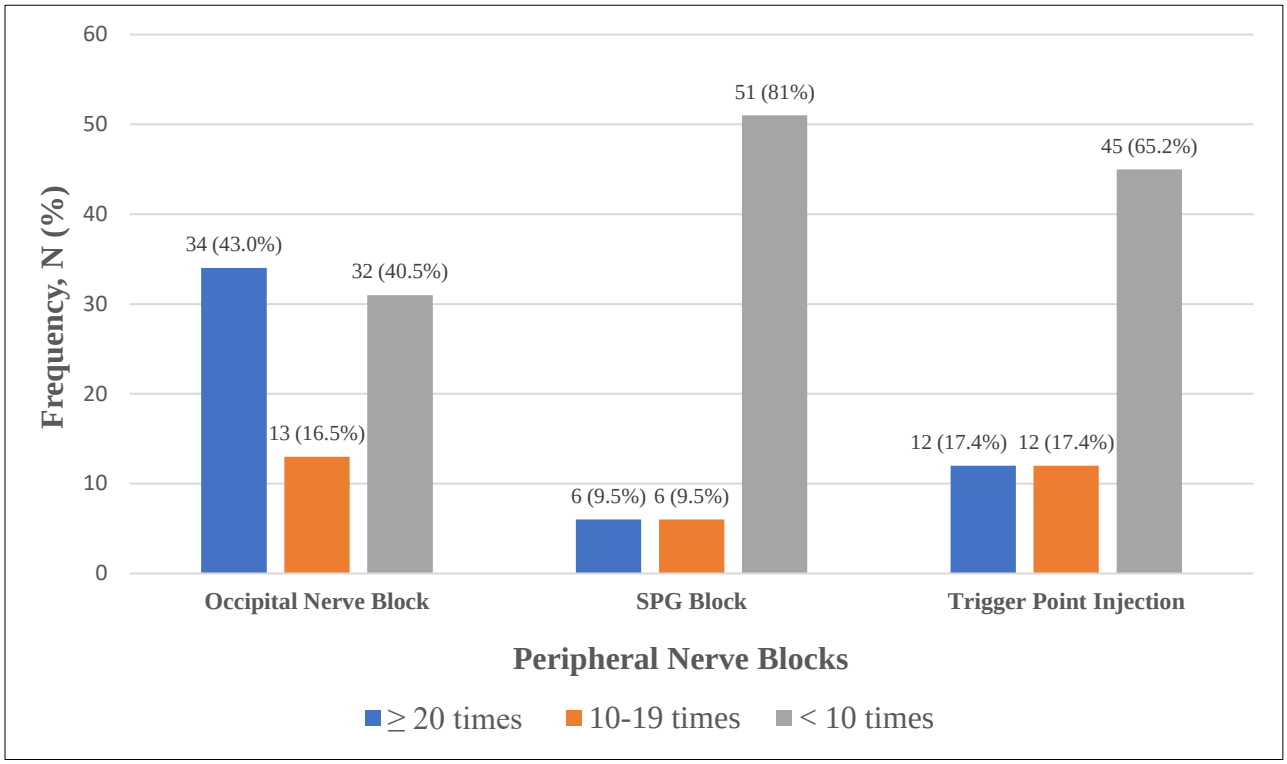
**CCFP: Canadian College of Family Physicians;
CCFP-EM: CCFP with a specialization in Emergency Medicine
FRCPC-EM: Fellow of the Royal College of Physicians and Surgeons of Canada in Emergency Medicine

Figure 4.2 Current Routine Practice for Benign Headaches – Frequency of use of Pharmacotherapies (N=144)



* IV or ORAL coadministration of ketorolac and a dopamine antagonist
**Other: dexamethasone was most frequently reported

Figure 4.3 Peripheral Nerve Block Use among Canadian Emergency Physicians (N=80)



*Occipital Nerve Block: N=79
Sphenopalatine Ganglion (SPG) Block: N=63
Trigger Point Injection: N=69

Table 4.2 Perspectives on Peripheral Nerve Blocks among Experienced Emergency Physicians (N=80)

Characteristics	Total N (%)
Effectiveness	
Agree	43 (55.1)
Disagree	9 (11.5)
N/A – Have not done enough PNBs to answer	26 (33.3)
Safety	
Agree	68 (85.0)
Disagree	3 (3.8)
N/A – Have not done enough PNBs to answer	9 (11.3)
Preferred PNB for Benign Headache Subtypes:	
Migraine	
Occipital nerve block	14 (17.1)
SPG block	18 (22.2)
Trigger point injection	5 (22.0)
N/A – Would not consider for this headache	45 (54.9)
Tension	
Occipital nerve block	33 (36.3)
SPG block	4 (4.4)
Trigger point injection	27 (30.0)
N/A – Would not consider for this headache	27 (30.0)
Cluster	
Occipital nerve block	4 (8.2)
SPG block	6 (7.6)
Trigger point injection	2 (2.5)
N/A – Would not consider for this headache	67 (84.8)
Comfort Level	
Occipital nerve block	
Comfortable	63 (78.8)
Uncomfortable	7 (8.8)
N/A – Do not perform this routinely	10 (12.5)
SPG block	
Comfortable	26 (32.5)
Uncomfortable	22 (27.5)
N/A – Do not perform this routinely	32 (40.0)
Trigger point injection	
Comfortable	41 (51.3)
Uncomfortable	18 (22.5)
N/A – Do not perform this routinely	21 (26.3)
Significant pain reduction after giving a PNB	
Yes	62 (77.5)

PNB: Peripheral Nerve Block
SPG: Sphenopalatine Ganglion Block

Table 4.3 Emergency Physician Insight on Design Features of a Future Trial (N=144)

	Total N (%)
Would you Consider PNBs as a First Line Treatment Option? N=140	
Yes	118 (84.3)
SPG block Preferred Mode of Administration, N=113	
Nasal cannula	6 (5.3)
Catheter device	1 (0.9)
Cotton tip applicator	18 (15.9)
Intranasal droplets	19 (16.8)
Other	1 (0.9)
N/A – I don't know	68 (60.2)
Most Clinically Meaningful Time to Reassess Pain, N=135	
15 mins	4 (2.96)
30 mins	41 (30.4)
60 mins	73 (54.1)
90 mins	11 (8.2)
120 mins	5 (3.7)
Other	1 (0.74)
Clinically significant improvement from baseline pain on a 10-point scale, N=136	
1 point	0 (0)
2 points	8 (5.9)
3 points	35 (25.7)
4 points	45 (33.1)
5 points	38 (27.9)
Other	10 (7.4)
Open to enrolling patients in a future trial, N=135	
Yes	94 (69.6)
No	19 (14.1)
Uncertain	22 (16.3)

PNB: Peripheral Nerve Block
SPG: Sphenopalatine Ganglion Block

Table 4.4 Comparison of Characteristics of Respondents and Non-respondents

Characteristic	**Responders N=179 N (%)**	**Non-Responders N=289 N (%)**	**Total N=468 N (%)**	***P*****
Geographic Location*				0.53
Western Canada	58 (32.4)	104 (36.0)	162 (34.6)	
Ontario	72 (40.2)	123 (42.6)	195 (41.7)	
Quebec	35 (19.6)	45 (15.6)	80 (17.1)	
Eastern Canada	14 (7.8)	17 (5.9)	31 (6.6)	
Language				0.08
English	147 (82.1)	254 (87.9)	401 (85.7)	
French	32 (17.8)	35 (12.1)	67 (14.3)	

*Geographic Location:

Western Canada: British Columbia, Alberta, Saskatchewan

Eastern Canada: Prince Edward Island, Nova Scotia, Newfoundland & Labrador, New Brunswick

**p-value derived from Chi-Square test

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4.9 Appendices

4.9.1 Appendix 4A – Current Practices for Benign Headache Disorders and Perspectives on Peripheral Nerve Blocks Among Emergency Physicians in Canada: Protocol for a National Survey

Authors:
*Dilan Patel[1,2], BSc
Monica Taljaard[1,2], PhD
Krishan Yadav[2,3], MD, MSc
Daniel James[2,3], MD
Jeffrey Perry[1,2, 3], MD, MSc

Author Affiliations:
1. School of Epidemiology and Public Health, University of Ottawa, K1G 5Z3 Ottawa, Ontario, Canada.
2. Ottawa Hospital Research Institute, ON K1Y 4E9 Ottawa, Ontario, Canada
3. Department of Emergency Medicine, University of Ottawa, Ontario, Canada

Version Date: July 29, 2021

ABSTRACT:

Background:

Treatment options for primary headache disorders, including acute and chronic migraine, tension headache and cluster headache in the emergency department (ED) are broad. The current standard of care, which includes nonsteroidal anti-inflammatory drugs (NSAIDs) and dopamine antagonists, may be considered suboptimal due to slow onset and often requires intravenous administration which may cause harmful side effects to patients. Other viable treatment options such as peripheral nerve blocks (PNBs), including occipital nerve blocks, sphenopalatine ganglion blocks and trigger point injections are less often utilized due to limited certainty on efficacy and safety from existing trials, compared to the current standard of care.

Objectives:

Our objective is to survey Canadian emergency physicians (EPs) to determine their current practice for benign headache disorders in the ED and determine EP perspectives on the use of PNBs for benign headache disorders in the ED.

Methods:

We will conduct a cross-sectional postal survey of a random sample of 500 EPs listed in the Canadian Medical Directory. We will utilize a modified Dillman technique including an initial survey with a small unconditional gift card ($5 Tim Horton's coffee card) and up to four additional reminder mailed surveys sent every three weeks to non-responders. For the last survey reminder, we will use a special contact with a courier envelope. A survey instrument will be developed in collaboration with emergency physicians and experts in pain management and appropriately translated to French for francophone physicians. We will pilot the survey and carry out cognitive interviews to determine content and face validity and non-verbal cues of our questionnaire and modify the instrument accordingly.

Discussion:

It is not currently known how primary headaches are treated in the ED given the wide variety of treatment options. This survey will provide insight on current practice patterns and determine if other known alternatives are currently being used. Results from this survey will provide useful information to guide the design of a future randomized controlled trial to test the effectiveness of alternate treatment options such as SPG blocks for the treatment of primary headache disorders in the ED.

BACKGROUND:

Headaches are a common neurological problem and can be disabling and negatively impact quality of life. The most common headache disorders in primary care are primary headaches, including migraine, tension-type headache and trigeminal autonomic cephalalgias (such as cluster headache) with

a global prevalence of 10%, 40% and 0.1% respectively. [1] These headaches are benign in nature and differ from secondary headaches. According to the Global Burden of Disease, migraine alone was the sixth highest cause worldwide of years lost to a disability, and headaches collectively ranked third.[2,3]

According to a US-based study, non-traumatic headaches account for 2.2% of emergency department (ED) visits per year; among this proportion, 98% are benign with the remainder being rare secondary headaches presenting in forms such as subarachnoid hemorrhage (SAH) or other life-threatening forms.[4] Diagnosing headaches in the ED is challenging and requires thoughtful consideration among emergency physicians (EPs). Primary headaches are difficult to diagnose mainly due to lack of awareness and impracticality of the international headache society (IHS) criteria; according to a ED based study, primary headaches were diagnosed for 16% of headache presentations, whereas 84% of headaches were not diagnosed.[5] Guidelines and policies have been implemented by the American College of Emergency Physicians to guide the management of acute headaches[6], as well as rules such as the Ottawa Subarachnoid Rule, to identify life-threatening forms of headache.[7–9]

Treatment options for primary headaches in the ED are diverse. First-line treatment options for primary headaches include nonsteroidal anti-inflammatory drugs (NSAIDs) such as intravenous (IV) ketorolac, oral or IV acetaminophen, antidopaminergic agents such as IV metoclopramide, prochlorperazine or haloperidol, oxygen therapy for cluster headaches and corticosteroids such as dexamethasone for reduction of headache recurrence.[10] Other medications which may be used consistently are IV fluids if dehydration is present, antiemetics such as dimenhydrinate which is useful against akathisia associated with prochlorperazine use, ondansetron, abortive therapy such as triptans, other butyrophenones such as droperidol, ergotamine, magnesium, IV sodium valproate and parenteral opioids.[10,11]

If first-line medications fail to relieve pain, recommended second-line medications include IV ketamine, IV propofol and peripheral nerve blocks (PNBs) such as the occipital nerve block (ONB),

sphenopalatine ganglion (SPG) block or intranasal lidocaine, and trigger point injections .[10] These first-line treatment options are recommended, however may act with significant delay, cause rare but potentially serious side effects or fail to control symptoms of headache. For example, haloperidol is known to cause extrapyramidal symptoms such as acute dystonia, akathisia, neuroleptic malignant syndrome, parkinsonism, tardive dyskinesia and anticholinergic effects, among others.[12,13]

A controversial medication option is the use of parenteral opioids for the treatment of benign primary headaches in the ED. According to a US-based survey, opioids were administered or prescribed in over 50% of migraine visits in the ED.[14] Many societies and committees recommend against using opioids for migraine and other primary headaches.[14–16] Opioids are disadvantageous as a treatment option since their use has been associated with increased frequency of recurrent ED visits, can impair the effectiveness of other migraine treatments, promotes chronic migraine and medication overuse headache and is associated with more psychiatric disorders when dependence is built on opioid use.[17] The prevalence of administration or prescription of opioids as a first line treatment for benign headache disorders in the ED among EPs is Canada is currently unknown.

PNBs which target peripheral nerves in the head and neck have gained recent interest for the optimal management of primary headaches in the ED. PNBs are understudied and potentially less often utilized as a treatment option in the ED. These minor bedside procedures involve a subcutaneous local injection of a small volume of a local anesthetic agent to target areas such as the greater or lesser occipital nerve, or sphenopalatine ganglion to promote neural blockade and break the pain cycle. Randomized controlled trials (RCTs) have been conducted to study the efficacy and safety of occipital nerve blocks on various forms of headache.[18–22] Several RCTs currently exist which study SPG blocks or intranasal administration of anesthetics[23–29]; the results are mixed, some trials found SPG blocks to provide statistically significant pain relief[23,25,27,28] and some found no difference compared to placebo.[26,29] To our knowledge, no trial currently exists which studies the SPG block or

intranasal lidocaine in Canada among the adult population for benign headaches in the ED. The SPG block is the least invasive of the PNBs especially with its intranasal route of administration, compared to the subcutaneous injection across the scalp of occipital nerve blocks or trigger point injections. For this reason, we also seek to investigate EP perspectives and attitudes towards using PNBs for benign headaches in the ED. Results from this survey will lay the foundation to study SPG blocks in the form of an RCT in Canada to potentially achieve a more successful and faster management of benign primary headaches in the ED compared to current standard of care.

OBJECTIVES:

The primary objective of this survey is to understand current practice patterns for benign primary headaches among EPs. This objective will provide insight into unanswered and important questions such as if EP's cotreat primary headaches with ketolorac and dopamine antagonists, if dexamethasone is used to prevent headache recurrence and the frequency of opioid use across Canada.

Secondary objectives are to determine EP perspectives on PNBs in terms of frequency of use, effectiveness, preference, and comfort level. Additionally, we will further investigate the SPG block in terms of preferred route of administration and inquire about the optimal time point to reassess pain after giving a PNB. Lastly, we will inquire about the minimal clinically important reduction in pain on a standard pain scale to safely discharge a patient presenting with a benign headache, home. This will inform the choice of an effect size to use in the sample size calculation for the future trial.

METHODS:

Study design and Setting:

We plan to conduct a national postal survey of a random sample of 500 Canadian EP's listed in the Canadian Medical Directory[30] according to a modified Dillman's tailored design method for survey design and administration.[31] We will use simple random sampling to select our sample.

Survey instrument construction:

The survey instrument will be developed in collaboration with physicians consisting of clinical experts in emergency medicine and pain medicine. The survey will be piloted with a random sample of 20 EP's and revised based on feedback. The survey should take 10-15 minutes to complete and will consist of binary questions (yes/no answers) and likelihood questions (i.e., always, most of the time, some of the time, almost never, never) on Likert scales. Survey questions will capture demographic data such as EP level of experience and address the following: 1) Current practices for benign headache assessment and treatment in the ED; 2) Challenges and limitations of current practice if any; 3) Perspectives on PNBs, specifically the SPG block; 4) The optimal time to reassess pain after administering a PNB; 5) The minimal clinically important relief of pain for safe discharge home.

We will pilot the first draft of the survey instrument and perform cognitive interviews as a psychologically derived method to understand how individuals respond to our questionnaire prior to administering the survey. Based on this interview, we will modify questions accordingly based on feedback and reactions to questions.

The survey instrument will be translated to French by a research coordinator fluent in the language, for francophone physicians, and approved by language services

Data Collection Strategy:

The survey will be administered according to the following procedure: (i) initial survey with an incentive ($5 Tim Horton's gift card) with the first survey and (ii) a reminder of survey completion through a new survey instrument, every three weeks for a total of four times, with the final notification using a special contact (e.g., Xpress post). Previous surveys have demonstrated >50% response rates using these methods.[32–34] For letters that are returned to sender due to unknown or outdated address, we will search the College of Physicians and Surgeons or equivalent in their respective jurisdiction to determine if there has been a change in primary practice location and attempt to re-send to their current practice location.

Survey responses and data will be input into Microsoft Excel v. 16 and statistical analyses will be conducted using SAS v. 9.4 (SAS Institute Inc. Cary, NC, USA). Incentives will be provided for survey respondents up front and attached with the mail in survey. All data management and study coordination will be at the Ottawa Hospital Research Institute.

Sub-studies

We will conduct a sub-study with half of the survey respondents (n = 250) receiving hand-signed recruitment and reminder letters and the other half of the survey respondents receiving electronically signed recruitment and reminder letters. The rationale for this is to determine if there is a difference in response rates between hand signatures compared to electronic signatures. This would provide useful recommendations for future postal surveys.

Analysis and Sample Size Calculation:

We will use descriptive statistics to describe the results from the survey including and frequencies and percentages for categorical variables. Comparisons will be conducted using chi-squared tests for categorical variables (i.e. differences based on EP level of experience).

A random sample of 500 emergency physicians listed in the Canadian Medical Directory will be surveyed. The large sample size will reduce sampling error and improve generalizability. The random sample will be selected using a computer-generated randomization sequence. A random sample of 500 EP's with a response rate of 50% is adequate to estimate the primary outcome (i.e., the proportion of survey respondents who use each class of drugs "always" or "most of the time") using a two-sided 95% confidence interval with a margin of error no greater than 6.2% assuming the most conservative prevalence estimate of 0.5.

ETHICAL CONSIDERATIONS:

Prior to collecting any data, this protocol will be reviewed by the Ottawa Health Science Network Research Ethics Board. In the cover letter of our designed survey, we will state that

participation is voluntary and survey responses will be kept confidential. Responding to a survey will be considered implied consent. We will keep sensitive information such as personal identifiers confidential and will be store separately from the data collected in the survey instrument.

CLINICAL IMPLICATIONS

Since headache presentations are prevalent and complex with multiple treatment options, it is important to understand frequently used medications in an EP's treatment plan across Canada. Based on this survey, we would have a better sense of a Canada-wide EP perspective on commonly used treatment methods for benign headache disorders, and insights on alternative treatments such as PNBs. We hope to fill the gap in headache treatment by providing evidence on current treatments and insight towards the SPG block which may be faster and more effective at relieving pain and reduce the use of opioid and other medications with known side effects.

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4.9.2 Appendix 4B - Ottawa Health Sciences Network Research Ethics Board Approval Letter

The Ottawa Hospital | L'Hôpital d'Ottawa
RESEARCH INSTITUTE | INSTITUT DE RECHERCHE

June 07, 2021

Ottawa Hospital - Civic Campus
Department of Emergency Medicine
F6, Room 647
1053 Carling Avenue
Ottawa, ON K1Y 4E9

Re: OHRI Institutional Approval for Ottawa Health Science Network Research Ethics Board (OHSN-REB) Submission

Protocol ID#: 20210212-01H;

Current Practices for Benign Headache Disorders and Perspectives on Peripheral Nerve Blocks Among Emergency Physicians in Canada: Protocol for a National Survey

Dear Dr.

This letter serves as **Ottawa Hospital Research Institute (OHRI)** Institutional Approval for the above-referenced study. Please maintain this documentation in your investigator study file.

Based on the information you provided about this study through the Clinical Research Registration Form, you have satisfied the requirements for institutional (OHRI) approval. This includes initial research ethics approval by OHSN-REB, appropriate departmental/service area notifications and execution (fully signed versions) of all agreement(s) required to begin the study locally. Please note there may be additional agreement(s) pending execution that are required to send funds, samples, or data to external sites, but are not required for you to begin your study locally.

Changes and/or additions to your study that may require additional agreement(s) or revisions to existing agreement(s) must be communicated to the OHRI Contracts Office. This should be undertaken simultaneously with any related OHSN-REB amendment submission.

Changes and/or additions to your study that affect various hospital/institution departments (e.g., pharmacy, Department of Medical Imaging, EORLA, EEG, etc.) must be communicated to the relevant departments.

As mentioned in the 'Response' tab of the Ethics application, you have 3 months from the date of initial OHSN-REB approval to submit French documents including the translation certificate to OHSN-REB through the Translated Documents section of the ethics application (if applicable).

Should you have any questions, please contact

Director, Clinical Research Administration
Ottawa Hospital Research Institute | Institut de recherche de l'Hôpital d'Ottawa

Civic Campus, Box 675, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9

4.9.3 Appendix 4C – Recruitment Letter

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

ENGLISH RECRUITMENT LETTER

Current Practices for Benign Headache Disorders and Perspectives on Peripheral Nerve Blocks Among Emergency Physicians in Canada: A National Survey

Subject Line: Invitation to participate in a study on current practice for benign headache disorders among emergency physicians in Canada.

Dear Colleague,

This letter is being sent to you by Dilan Patel who is currently a Master in clinical epidemiology student being supervised by an emergency physician scientist at The Ottawa Hospital, Dr. Jeffrey Perry. This letter is with regards to a research study that we are conducting. Participation is voluntary.

The overall goal of this study is to assess current practice patterns for benign headaches among Canadian emergency physicians and perspectives on peripheral nerve blocks. Current treatment options for benign headaches in the emergency department (ED) are diverse. Results from this study will provide the foundation for studying alternative treatment options for benign headaches in the ED.

This questionnaire should take about **10 minutes** to complete. Enclosed with this survey is a gift card as gratitude for your time.

There are no foreseeable risks or discomforts associated with your involvement in this study.

Your responses will remain strictly confidential, and no participant identifiers will appear in any publication or presentation resulting from this study. Please note that there will be no written consent for this study. By completing the questionnaire, you are providing your consent to participate in the study. An information sheet is enclosed with more information about this study.

We will send a reminder letter every three weeks for a total of four times if we have not received your returned questionnaire.

The study is filed with Ottawa Health Science Network Research Ethics Board (OHSN-REB) as 20210212-01H. If you have any questions about your rights as a study participant, you may contact the Chairperson of the OHSN-REB at +1 613-798-5555, extension 16719.

If you have any questions regarding the study, please contact the Research Fellow, Dilan Patel at

Thank you for your time.
Sincerely,

Dilan Patel, MSc (c), BSc
Research Coordinator
Department of Emergency Medicine
The Ottawa Hospital Research Institute School of Epidemiology and Public Health, University of Ottawa

Dr. Jeffrey Perry, MD, MSc
Professor, Department of Emergency Medicine and School of Epidemiology and Public Health, University of Ottawa
Senior Scientist, The Ottawa Hospital Research Institute

May 27, 2021

4.9.4 Appendix 4D – Reminder Letter

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

ENGLISH REMINDER LETTER

Current Practices for Benign Headache Disorders and Perspectives on Peripheral Nerve Blocks Among Emergency Physicians in Canada: A National Survey

Subject: Reminder of invitation to participate in a study on current practice for benign headache disorders among emergency physicians in Canada.

Dear Colleague,

This reminder letter is being sent to you by Dilan Patel who is currently a Master in clinical epidemiology student being supervised by an emergency physician scientist at The Ottawa Hospital, Dr. Jeffrey Perry. Participation is voluntary.

You recently received an invitation **[X weeks ago]** to participate in a research survey regarding current practices for benign headaches and perspectives on peripheral nerve blocks among emergency physicians in Canada. To the best of our knowledge, we have not received your completed questionnaire. I would truly appreciate your consideration in completing the enclosed questionnaire, **which should take about 10 minutes to complete.** We ask that you then return the questionnaire in the postage-paid, addressed envelope.

In brief, the overall goal of this study is to determine patterns in the practice of benign headaches in the emergency department (ED), given the diverse treatment options currently available. By completing the survey, you are providing your consent to participate in the study.

This is the **[N]** reminder. We will send a reminder letter every three weeks for a total of four times if we have not received your returned questionnaire.

If you choose not to complete the questionnaire but you are open to being contacted by the research coordinator, or if you have any questions regarding the study, please contact the Research Fellow, Dilan Patel at

Thank you once again for you time.

Sincerely,

Dilan Patel, MSc (c), BSc
Research Coordinator
Department of Emergency Medicine
The Ottawa Hospital Research Institute
School of Epidemiology and Public Health, University of Ottawa

Dr. Jeffrey Perry, MD, MSc
Professor, Department of Emergency Medicine and School of Epidemiology and Public Health, University of Ottawa
Senior Scientist, The Ottawa Hospital Research Institute

June 8, 2021

4.9.5 Appendix 4E – Final Reminder

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

ENGLISH FINAL REMINDER LETTER

Current Practices for Benign Headache Disorders and Perspectives on Peripheral Nerve Blocks Among Emergency Physicians in Canada: A National Survey

Subject: Final reminder of invitation to participate in a study on current practice for benign headache disorders among emergency physicians in Canada.

Dear Colleague,

This final reminder letter is being sent to you by Dilan Patel who is currently a Master in clinical epidemiology student being supervised by an emergency physician scientist at The Ottawa Hospital, Dr. Jeffrey Perry. Participation is voluntary.

You recently received an invitation **12 weeks ago** to participate in a research survey regarding current practices for benign headaches and perspectives on peripheral nerve blocks among emergency physicians in Canada. To the best of our knowledge, we have not received your completed questionnaire. I would truly appreciate your consideration in completing the enclosed questionnaire, **which should take about 10 minutes to complete.** We ask that you then return the questionnaire in the postage-paid, addressed envelope.

In brief, the overall goal of this study is to determine patterns in the practice of benign headaches in the emergency department, given the diverse treatment options currently available.

By completing the survey, you are providing your consent to participate in the study.

If you choose not to complete the questionnaire but you are open to being contacted by the research coordinator, or If you have any questions regarding the study, please contact the Research Fellow, Dilan Patel at

Thank you once again for you time.

Sincerely,

Dilan Patel, MSc (c), BSc
Research Coordinator
Department of Emergency Medicine
The Ottawa Hospital Research Institute
School of Epidemiology and Public Health, University of Ottawa

Dr. Jeffrey Perry, MD, MSc
Professor, Department of Emergency Medicine and School of Epidemiology and Public Health, University of Ottawa
Senior Scientist, The Ottawa Hospital Research Institute

December 22, 2020

4.9.6 Appendix 4F – Survey Instrument

Questionnaire ID

Current Practice for Benign Headaches in the Emergency Department & Perspectives on Peripheral Nerve Blocks

Are you currently treating adults in emergency medicine?

☐ Yes ☐ No *If 'No', please return the survey in the pre-paid envelope provided.*

CURRENT PRACTICE FOR BENIGN HEADACHES – DRUG THERAPIES

We are seeking your valued opinion on how often you use various therapies to treat benign headaches in the emergency department (ED). In this survey, benign headaches are defined as any non life-threatening headache (e.g., acute or chronic migraine, tension headache) where a secondary cause has been ruled out.

1. Please indicate your current pharmacological practice for treating benign headache disorders in the ED

	Always	Most of the time	Some of the time	Almost never	Never
a) Intravenous (IV) NSAID (e.g., ketorolac)	☐	☐	☐	☐	☐
b) ORAL Non-Steroidal Anti-Inflammatory Drug (NSAID) (e.g., Naproxen, ibuprofen)	☐	☐	☐	☐	☐
c) ORAL acetaminophen	☐	☐	☐	☐	☐
d) IV dopamine antagonist (e.g., metoclopramide, chlorpromazine, prochlorperazine, promethazine, haloperidol, other)	☐	☐	☐	☐	☐
e) ORAL dopamine antagonist (e.g., metoclopramide, chlorpromazine, prochlorperazine, promethazine, haloperidol, other)	☐	☐	☐	☐	☐
f) IV or ORAL Co-administration of ketorolac and a dopamine antagonist	☐	☐	☐	☐	☐
g) Triptans	☐	☐	☐	☐	☐
h) Other antiemetics (e.g., dimenhydrinate, ondansetron)	☐	☐	☐	☐	☐
i) Dihydroergotamine (DHE)	☐	☐	☐	☐	☐
j) Oral opioids, (e.g., tramadol, morphine, hydromorphone)	☐	☐	☐	☐	☐
k) Parenteral opioids (e.g., tramadol, morphine, hydromorphone, fentanyl)	☐	☐	☐	☐	☐
l) IV Sodium valproate	☐	☐	☐	☐	☐
m) IV Fluid Boluses ≥ 500 mL	☐	☐	☐	☐	☐
n) Oxygen therapy for cluster headaches	☐	☐	☐	☐	☐
o) IV propofol	☐	☐	☐	☐	☐
p) IV ketamine	☐	☐	☐	☐	☐
q) IV magnesium	☐	☐	☐	☐	☐
r) Other drug therapy not listed above (please specify):_____	☐	☐	☐	☐	☐

2. Do you alter your ED pharmacological management based on type of headache you believe a patient may have (e.g., migraine versus tension/benign headache after ruling out a serious etiology)?
☐ Yes ☐ No

a. If yes, how? _____

_____

_____

_____

PERSPECTIVES ON PERIPHERAL NERVE BLOCKS

In this survey, peripheral nerve blocks are defined as greater or lesser occipital nerve blocks, sphenopalatine ganglion (SPG) blocks/intranasal lidocaine or trigger point injections.

3. Have you ever used a peripheral nerve block in your treatment plan for benign headache disorders?

☐ Yes ☐ No (If you answer 'No', please move to question 4 on page 3)

a. If yes, how frequently have you used <u>each</u> peripheral nerve block for benign headaches in your practice?

	≥ 20 times	10-19 times	≤ 10 times
i) Occipital nerve block	☐	☐	☐
ii) Sphenopalatine ganglion (SPG) block/intranasal lidocaine	☐	☐	☐
iii) Trigger point injection	☐	☐	☐

b. If yes, do you agree or disagree that alternative treatments such as peripheral nerve blocks could be *more effective* than current standard of care when treating benign headache disorders in the ED?

☐ Agree ☐ Disagree ☐ I have not done enough peripheral nerve blocks to answer.

c. If yes, do you agree or disagree that peripheral nerve blocks are *safe* to use when treating benign headaches in the ED?

☐ Agree ☐ Disagree ☐ I have not done enough peripheral nerve blocks to answer.

d. If yes, do you have a preferred peripheral nerve block for treating various benign headaches?

i) Migraine
☐ Occipital nerve block ☐ SPG block/intranasal lidocaine ☐ Trigger point injection ☐ N/A – I would not consider for this type of headache

ii) Tension
☐ Occipital nerve block ☐ SPG block/intranasal lidocaine ☐ Trigger point injection ☐ N/A – I would not consider for this type of headache

iii) Cluster headache
☐ Occipital nerve block ☐ SPG block/intranasal lidocaine ☐ Trigger point injection ☐ N/A – I would not consider for this type of headache

e. **If yes, how would you describe your comfort level when administering a peripheral nerve block?**

i) Occipital nerve block

☐ Very comfortable ☐ Comfortable ☐ Uncomfortable ☐ Very uncomfortable ☐ N/A - I do not perform this nerve block routinely

ii) SPG block/intranasal lidocaine

☐ Very comfortable ☐ Comfortable ☐ Uncomfortable ☐ Very uncomfortable ☐ N/A - I do not perform this nerve block routinely

iii) Trigger point injection

☐ Very comfortable ☐ Comfortable ☐ Uncomfortable ☐ Very uncomfortable ☐ N/A - I do not perform this nerve block routinely

f. **In your experience, do most patients experience a significant reduction in pain when given a peripheral nerve block?**

☐ Yes ☐ No

i) If yes, this significant reduction in pain was observed when administering: (check all that apply)

☐ Greater or lesser occipital nerve block ☐ SPG block/intranasal lidocaine ☐ Trigger point injection

4. Given sufficient evidence on effectiveness and safety from a randomized controlled trial, would you consider using a peripheral nerve block in the future as a *first line* treatment option for benign headaches?

☐ Yes ☐ No

If no, why not? _____

5. If you perform the SPG block/intranasal lidocaine, which route of administration of anesthetic would you be most comfortable with? (check one)

☐ Nasal cannula ☐ Catheter device ☐ Cotton tip applicator ☐ Intranasal droplets ☐ N/A - I do not know

☐ Other: _____

6. In a planned future trial comparing the SPG block/intranasal lidocaine to standard of care for benign headaches:

a) When is the most clinically meaningful time to reassess the patient's pain?

☐ 15 min ☐ 30 min ☐ 60 min ☐ 90 min ☐ 120 min ☐ Other (please specify):_____

b) What would you consider a clinically significant improvement from baseline pain to the time you answered in question 6a), on a 10-point pain scale?

☐ 1 points ☐ 2 points ☐ 3 points ☐ 4 points ☐ 5 points ☐ Other (please specify):_____

c) Would you consider enrolling your patients with a benign headache into such a study?

☐ Yes ☐ No ☐ Uncertain (please specify):_____

PHYSICIAN DEMOGRAPHICS AND PRACTICE SETTING

Please answer all questions

8. What is your gender?

☐ Male ☐ Female ☐ Other (specify):_____ ☐ Prefer not to say

9. How many years have you been practicing emergency medicine post-residency?

☐ 1-4 ☐ 5-9 ☐ 10-19 ☐ 20 or more

10. Please check ALL the Canadian credentials you currently hold:

☐ CCFP ☐ Other, if other please specify credentials: _____

☐ CCFP-EM

☐ FRCPC-EM

11. In what setting do you perform MOST of your emergency medicine clinical activity?

☐ Academic Health Centre ☐ Other: _____

☐ Community / District General Hospital: Teaching

☐ Community / District General Hospital: Non – Teaching

☐ Rural

12. Approximately how many patient visits, per year, are made to the ED you worked at MOST frequently?

☐ < 30, 000

☐ 30,000 – 59,999

☐ 60,000 – 79, 999

☐ > 80, 000

End of Survey

Please fold and return this survey to a mailbox in the pre-paid envelope provided.
Thank you for taking the time to complete this survey!
Your input is appreciated.

Additional comments: **Please feel free to add comments or feedback in the space provided below:**

4.9.7 Appendix 4G – Information Sheet

The Ottawa Hospital Research Institute | L'Hôpital d'Ottawa Institut de recherche

uOttawa

Information Sheet

Study Title: Current Practices for Benign Headache Disorders and Perspectives on Peripheral Nerve Blocks Among Emergency Physicians in Canada: A National Survey

Principal Investigator: Dr. Jeffrey Perry

OHSN-REB Number: 20210212-01H

You are being asked to participate because you are a practicing Canadian emergency physician. This study examines current practice patterns for benign headaches among Canadian emergency physicians and perspectives on peripheral nerve blocks. Current treatment options for benign headaches in the emergency department (ED) are diverse. Results from this study will provide the foundation for studying alternative treatment options for benign headaches in the ED.

There are no conflicts of interest to declare related to this study.

Your participation in this study will require the completion of a survey. The survey asks questions about your current practice for treating benign headaches in the ED and your perspective on alternative treatments. This should take approximately 10 minutes of your time.

The information you provide is for research purposes only. Some of the questions are personal. You can choose not to answer questions if you wish.

You do not have to be in this study if you do not want to be. You can choose to end your participation in this research (called withdrawal) at any time without having to provide a reason. The decision will not affect your employment.

If you decide to leave the study, you can ask that the information that was collected not be used for the study. Let the research team know if you choose this.

Participation involves minimal risk to you. Some of the questions may however make you feel uncomfortable.

You may not receive direct benefit from participating in this study. We hope the information learned from this study will help patients with benign headache disorders in the future.

Records identifying you at this centre will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Authorized representatives of the following organizations may look at your original (identifiable) research records at the site where these records are held, to check that the information collected for the study is correct and follows proper laws and guidelines.

- The Ottawa Health Science Network Research Ethics Board who oversees the ethical conduct of this study.
- Ottawa Hospital Research Institute, to oversee the conduct of research at this location.

Information that is collected about you for the study (called study data) may also be sent to the organizations listed above. Your name, address, email, or other information that may directly identify you will not be used. The records received by these organizations may contain your questionnaire ID and gender.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be used in analyses and will be published and presented to the scientific community at meetings and in journals.

Your de-identified data from this study may be used for other research purposes. If your study data is shared with other researchers, information that links your study data directly to you will not be shared.

Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

As a token of our appreciation, you will be given a [$5] gift card to Tim Horton's for your participation in this study. The gift card is enclosed with this survey.

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of the results of this study, please contact the study coordinator.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

If you have any questions about taking part in this study, you may contact the Research Fellow, Dilan Patel at

If you have questions about your rights as a participant or about ethical issues related to this study, you can talk to someone who is not involved in the study at all. Please contact The Ottawa Health Science Network Research Ethics Board. Chairperson at

By completing this survey your consent to participate is implied.

4.9.8 Appendix 4H – Certificate of French Translation

The Ottawa Hospital | L'Hôpital d'Ottawa

Note to File

Date: **July 20, 2021**

RE: **20210213-01H** – Current Practices for Benign Headache Disorders and Perspectives on Peripheral Nerve Blocks Among Emergency Physicians in Canada: A National Survey

Subject: **Certification of Translation**

Please be advised that the translation from English to French is a true and accurate translation of the following:

- Reminder Letter, December 22, 2020
- Recruitment Letter, dated May 27, 2021
- Headache Survey, June 8, 2021
- Final Reminder, December 22, 2020
- Information Sheet, dated May 27, 2021

Name of Translator

Signature of Translator

July 20, 2021

***Please ensure you provide this *Certificate of Translation* with your submission to REB.**

Inspired by research. Driven by compassion. Inspiré par la recherche. Guidé par la compassion.

4.9.9 Appendix 4I – Supplemental Information

Table 4I.1 Raw Data: Current Routine Practice for Benign Headaches by Respondents (N=144)

Drug therapy	**Always N (%)**	**Most of the Time N (%)**	**Some of the Time N (%)**	**Almost Never N (%)**	**Never N (%)**
IV Dopamine Antagonist	20 (14.1)	78 (54.9)	39 (27.5)	4 (2.8)	1 (0.7)
Oxygen therapy	42 (30)	39 (27.9)	28 (20.0)	20 (14.3)	11 (7.9)
IV/ORAL Combination Therapy*	9 (6.3)	69 (47.9)	38 (26.4)	11 (7.6)	17 (11.8)
IV NSAID	11 (7.8)	65 (45.8)	41 (28.9)	11 (9.9)	14 (14.5)
IV Fluid Boluses ≥ 500 mL	16 (11.5)	59 (42.5)	41 (29.5)	17 (12.2)	6 (4.3)
Acetaminophen	33 (23.2)	40 (28.2)	56 (39.4)	11 (7.8)	2 (1.4)
ORAL NSAID	5 (3.5)	51 (35.7)	72 (50.4)	12 (8.4)	3 (2.1)
Other antiemetics	0 (0)	25 (17.9)	70 (50.0)	37 (26.4)	8 (5.7)
ORAL Dopamine Antagonist	1 (0.7)	6 (4.2)	31 (21.7)	67 (46.9)	38 (26.6)
Triptans	0 (0)	5 (3.6)	34 (24.6)	54 (39.1)	45 (32.6)
IV Magnesium	0 (0)	2 (1.4)	14 (10)	18 (12.9)	106 (75.7)
Other**	0 (0)	3 (10.3)	10 (34.5)	4 (13.8)	12 (41.4)
Parenteral opioids	1 (0.7)	1 (0.7)	35 (24.7)	72 (50.7)	33 (23.2)
IV Sodium valproate	1 (0.7)	0 (0)	4 (2.8)	9 (6.4)	127 (90.1)
Dihydroergotamine	0 (0)	0 (0)	21 (14.8)	45 (31.7)	76 (53.5)
ORAL opioids	0 (0)	0 (0)	26 (18.6)	76 (54.3)	38 (27.1)
IV Propofol	0 (0)	0 (0)	6 (4.2)	21 (14.8)	115 (81.0)
IV Ketamine	0 (0)	0 (0)	3 (2.1)	31 (21.8)	108 (76.1)

IV: Intravenous; NSAID: Non-Steroidal Anti-Inflammatory Drug

* Coadministration of ketorolac and a dopamine antagonist

**Other: dexamethasone was most frequently reported

Table 4I.2 Current Routine Practice for Benign Headaches by Respondents Collapsed into High and Low (N=144)

Drug therapy	**High† N (%)**	**Low* N (%)**
IV Dopamine Antagonist	98 (69.0)	44 (31.0)
Oxygen therapy for cluster headaches	81 (57.9)	59 (42.1)
IV or ORAL Coadministration of ketorolac and a dopamine antagonist	78 (54.2)	66 (45.8)
IV NSAID	76 (53.5)	66 (46.5)
IV Fluid Boluses ≥ 500 mL	75 (54.0)	64 (46.0)
Acetaminophen	73 (51.4)	69 (48.6)
ORAL NSAID	56 (39.2)	87 (60.8)
Other antiemetics	25 (17.9)	115 (82.1)
ORAL Dopamine Antagonist	7 (4.9)	136 (95.1)
Triptans	5 (3.6)	133 (96.4)
IV magnesium	2 (1.4)	138 (98.6)
Other**	3 (10.3)	26 (89.7)
Parenteral opioids	2 (1.4)	140 (98.6)
IV Sodium valproate	1 (0.7)	140 (99.3)
Dihydroergotamine	0 (0)	142 (100)
ORAL Opioids	0 (0)	140 (100)
IV propofol	0 (0)	142 (100)
IV ketamine	0 (0)	142 (100)

IV: Intravenous; NSAID: Non-Steroidal Anti-Inflammatory Drug
†High: Categories "Always" and "Most of the time" were collapsed to represent high frequency
*Low: Categories "Some of the time", "Almost never" and "Never" were collapsed to represent low frequency
**Other: dexamethasone was most frequently reported

Chapter 5: Effect of Hand Versus Electronic Signatures on Response Rates in Postal Surveys: A Randomized Controlled Trial

Authors:
*Dilan Patel[1,2], BSc
Monica Taljaard[1,2], PhD
Krishan Yadav[2,3], MD, MSc
Michael Hickey[4], MD, MSc
Jeffrey J. Perry[1,2,3], MD, MSc

Author Affiliations:
1. School of Epidemiology and Public Health, University of Ottawa, K1G 5Z3 Ottawa, Ontario, Canada.
2. Ottawa Hospital Research Institute, ON K1Y 4E9 Ottawa, Ontario, Canada
3. Department of Emergency Medicine, University of Ottawa, Ontario, Canada
4. Department of Medicine, University of Toronto, Toronto, Ontario, Canada

*Corresponding Author
Dilan Patel
ORCID: 0000-0002-2921-0576
Clinical Epidemiology Program, Department of Emergency Medicine
Ottawa Hospital Research Institute
The Ottawa Hospital, Civic Campus
1053 Carling Ave., Ottawa, ON, K1Y 4E9

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The authors have no conflicts of interest to declare.

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Author Contributions:

This manuscript was conceptualized by DP, MT and JJP. Data collection and research coordination was carried out by DP. Statistical analysis was conducted by DP and MT. This manuscript was supervised by JJP and MT. The original draft was written by DP. The writing, reviewing, and editing of this manuscript was conducted by DP, MT, KY, MH and JJP.

5.1 Abstract

Objectives:

Hand signatures offer a more authentic personalization which carries over to a sense of trust, although are costly and time consuming when considering large postal surveys. The objective of this study was to compare response rates when using either hand-signed or electronic-signed letters in a postal survey.

Methods:

We embedded this randomized controlled trial within a national cross-sectional postal survey of emergency physicians in Canada. The survey aimed to describe current practice patterns with respect to primary headache disorders. We randomly sampled 500 emergency physicians listed in the Scott's Canadian Medical Directory, 2019 edition. Using computer-generated random numbers, physicians were allocated to receiving either hand-signed (n = 250) or electronic signed (n = 250) letters. The initial mailout contained a $5 Tim Hortons™ coffee card with the invitation letter. Four reminders were sent to non-responders every three weeks. The same type of signature was used for the initial invitation and subsequent reminders. The primary outcome was the survey response rate.

Results:

Among 500 physicians invited, 32 invitations were undeliverable. Among the remaining 468 physicians, 231 had been allocated to the hand-signed group and 237 to the electronic signed group. The response rate in the hand-signed group was 83 (35.9%) versus 96 (40.3%) in the electronic-signed group (absolute difference in proportions -4.6%, 95% CI: -13.4% to 4.2%).

Conclusion:

There was no significant difference in physician response rate between hand-signed and e-signed cover letter and reminder letters. Electronic signatures should be used in future postal surveys among physicians to save on time and labour without impacting response rates.

5.2 Introduction

5.2.1 Background

Physician surveys are often used to obtain information about their perspectives and attitudes towards clinical problems. A major challenge with physician surveys is obtaining an adequate response rate. Postal surveys typically have a higher response rate (up to 20% higher) compared to other modes of administration such as internet-based surveys, but are more costly and labour intensive.[1,2] There is evidence to suggest that physician response rates have been declining with time.[1,3] Among the reasons for declining response rates are lack of time during core working hours and gatekeepers such as receptionists who may perceive the survey as irrelevant and prevent it from reaching the recipient.[1] Exploring avenues to optimize response rates with respect to labour and cost is important.

The Dillman's Tailored Design Method provides recommendations on the optimal construction of surveys using various modes of administration.[4] These methods are well established in the literature and have shown response rates ranging from 50% to 65% when used as standalone mode of survey administration.[4] Methods for optimizing postal surveys are continuously being explored to lower expenses and reduce labour. In our experience, the costs and labour involved in a postal survey include i) printing large amounts of paper for the survey instrument and supporting documentation; ii) costs associated with printing and purchasing envelopes; iii) costs associated with pre-stamping the pre-paid envelopes for each contact, the $5 incentive at initial mailout and sending the overall package; iv) folding printed materials into thirds and inserting into envelopes; v) manual data entry; and vi) hand signing of recruitment and reminder letters.

The effects of personalization on response rates has been previously explored: insertion of name and address and blue ink signatures in each letter compared to mass-copied letters with group salutations improved response rates from 3 to 12% for the general population.[5] It is unclear if these findings hold true in a specialized population of physicians. Although it is more labour intensive to hand-sign masses of letters for each contact point, hand signatures have a more attractive visual appeal, offer a more personalized effect, and carry over to a sense of trust which may contribute to a higher response rate. On the other hand, if hand-signed letters show no significantly higher response rate than electronically signed (e-signed) letters, this would be useful information and could reduce time and labour in future postal survey administration.

5.2.2 Objectives

The primary objective of this randomized trial embedded within a national postal survey was to determine if hand-signed letters resulted in a higher response rate compared to e-signed letters among Canadian emergency physicians.

We previously found some differences in response rates between French and English participants in Chapter 4. We therefore conducted a post-hoc exploratory subgroup analyses to compare the effect of e-signatures versus hand signatures between English and French participants.

5.3 Methods

5.3.1 Study Design and Participants

We used a national self-administered postal survey of emergency physicians listed in the 2019 Scott's Canadian Medical Directory, which is Canada's leading source for contact information and claims to list over 98% of practicing physicians with 97% address accuracy.[6] The results from the survey are reported in Chapter 4. The survey (Appendix 4F) was mailed to a random sample of 500 physicians. Physicians were eligible for the survey if they were currently

treating adults in emergency medicine. The questionnaire was two pages in length and consisted of 12 questions which took approximately 10 minutes to complete. The survey addressed emergency physicians' current practice for treating benign headache disorders in the emergency department and their perspectives and attitudes towards peripheral nerve blocks (PNBs). PNBs are minor bedside procedures which are sometimes used to treat primary headache disorders in the emergency department.

5.3.2 Outcome Measure

The primary outcome was the response rate, where a response was considered any physician who returned a partially or fully completed questionnaire. The denominator was considered all successfully delivered surveys (i.e., the number invited minus those returned undeliverable).

5.3.3 Intervention

Using computer-generated numbers in Microsoft Excel (Redmond, Washington, United States), we randomly assigned half (n = 250) of our random sample of 500 emergency physicians to receive hand-signed letters and the remaining half to receive e-signed letters. The letters at each mailout (initial mailout and reminders 1 to 4) were all either hand-signed or e-signed depending on each emergency physicians assigned group. In the hand-signature group, the same two investigators (DP and JJP) signed each letter in blue ink above printed names, credentials and affiliations. In the e-signed group, scanned electronic signatures (in black ink) of DP and JJP were placed above printed name, credentials, and affiliations at the bottom of each letter (Appendix 4C-E).

5.3.4 Survey Administration

The survey was administered according to a modified Dillman's method, including an initial mailout with an unconditional $5 Tim Horton's™ coffee card, either a hand-signed or e-signed recruitment letter, the survey instrument, an information sheet and a postage-paid envelope. We used four reminders sent every three weeks to non-responders with either hand-signed or e-signed reminder letters stating the number of weeks it has been since the last letter with a new survey instrument and a pre-paid return envelope. The final reminder was sent using Canada Post Xpresspost™ which guarantees delivery within 1-3 business days and is larger and more visually appealing in appearance. Surveys were administered in English or French according to recipients' language preference as reported by the Canadian Medical Directory.

5.3.5 Sample size rationale:

The sample size of 500 was sufficient to detect an absolute difference in the response rate between the hand-signed and e-signed groups of 6.2% with 80% power, assuming a response rate of 50% in the e-signed group and using a two-sided test at the 5% level of significance.

5.3.6 Data Analysis

Data from returned survey questionnaires were manually entered into Microsoft Excel (Redmond, Washington, United States). We assessed differences between respondents and non-respondents in geographical practice location in Canada and language preference using chi-squared tests. We used a chi-squared test to compare the response rates in the hand-signature and e-signed groups together with absolute and relative difference in proportions and a two-sided 95% confidence interval. All data analysis was conducted using Microsoft Excel (Redmond, Washington, United States) and SAS version 9.2 (SAS Institute, Cary, NC, USA).

For the exploratory subgroup analysis, we stratified results by language and obtained absolute differences in proportions. We also tested for a significant interaction effect using logistic regression.

5.4 Results

5.4.1 Response Rate

Figure 5.1 demonstrates the flow diagram for our study. We launched the survey in June 2021 and collected final responses in December 2021. From the 2,955 emergency physicians listed in the Canadian Medical Directory, we randomly selected 500 and assigned n = 250 into each of the hand-signed and e-signed groups. Thirty-two (32) surveys were returned undeliverable due to change in practice location, retired or other reasons. Of 468 delivered surveys (231 in the hand-signed and 237 in the e-signed group), we received 179 responses for an overall response rate of 38.2%. The response rate in the hand-signed group was 80 (35.9%) compared to 96 (40.3%) in the e-signed group (absolute difference in proportions -4.6%, 95% CI: -13.4% to 4.2%, relative difference: 0.89, 95% CI: 0.70 to 1.12).

5.4.2 Respondent Characteristics

Table 5.1 displays respondent demographics in the hand-signed and e-signed groups. Physician demographics were similar between the hand-signature and e-signed group. The majority of the respondents were male (61.8%), in practice for 10 or more years (80.6%) and had a Canadian College of Family Physicians with specialization in Emergency Medicine (CCFP-EM) designation (50%). Most emergency physicians practiced in Ontario (40.2%), British Colombia (21.2%) and Quebec (19.6%) and in an academic health centre or community/district teaching hospital (81.5%) which accommodates 60,000 or more emergency department visits per year (57.0%).

For the exploratory subgroup analysis comparing effect of the type of signatures between English and French participants (Table 5.2), the response rate among English participants was 68/200 (34%) in the hand-signed group compared to 79/201 (39.3%) in the e-signed group (absolute difference: -5.3%, 95% CI: -14.7% to 4.1%). Among French participants, the response rate was 15/31 (48.4%) in the hand-signed group compared to 17/36 (47.2%) in the e-signed group (absolute difference: 1.2%, 95% CI: -22.8% to 25.2%); p-value for statistical interaction P=0.61.

5.5 Discussion

Our randomized controlled trial embedded within a national postal survey was unable to demonstrate that hand-signatures have a higher response rate than e-signatures. This is an important finding for the methodology of future postal surveys as the time involved with hand-signing can be replaced with other less time-consuming methods such as e-signatures without negatively affecting response rates. In our survey, both investigators signed approximately 825 letters each, which involved several hours of monotonous labour. Based on our response rate and with 4 reminders to non-respondents, approximately 1825 signatures would be required if all respondents were to receive hand-signatures. Although hand-signatures appear valuable, this step is time consuming, and our results suggest this step may be replaced with e-signatures thus saving several hours of time and labour. Although we found no statistically significant difference, we note that the response rate was lower in the hand-signature group compared to e-signatures, which was unexpected. Hand-signatures offer a more authentic method of personalization which may carry over to sense of trust; we expected a higher response rate among this group.

A meta-analysis of randomized controlled trials of strategies that influence response rates to postal surveys among various disciplines, found a higher response rate amongst more personalized appearing letters compared to less personalized letters (OR 1.16, 95% CI: 1.06 to

1.28); however, only 5 of 48 studies included in the analysis compared hand-signatures against printed signatures.[7–9] A previous national postal survey conducted in 1999 with an overall response rate of 78.7% found no significant difference between the hand signed group and computer printed group (relative difference 1.01, 95% CI: 0.98 to 1.04).[8] Their method of postal administration differed from ours in that they only used two reminders, no incentives and no Xpress post (courier like delivery) in their final reminder. They did however use personal salutations whereas ours did not. Their study was conducted in the United Kingdom to members of the Royal College of Obstetricians. Our study is 20 years more recent and applicable to future postal surveys, especially for a specialized population of emergency physicians working in busy emergency departments across Canada. Additionally, an electronic signature in present-time looks similar to physical hand-signatures, compared to electronic signatures from the twentieth century.

Our study has several strengths. Our methods were adapted and improved from previous postal surveys using the Dillman's technique, such as inclusion of an unconditional $5 Tim Horton's™ coffee card with the initial mailout which has been shown to significantly improve response rates[10] and removal of pre-notification letters which have shown to result in lower response rates.[11] We also used additional measures to ensure physicians who have moved primary practice locations received their survey by verifying with the appropriate provincial regulatory body's website (e.g. College of Physicians and Surgeons of Ontario) of any updates to primary practice location before attempting to re-send letters that were undeliverable and returned to sender. Previous surveys have not documented this additional step and we found this beneficial in improving our response rate. Our findings may be generalizable to emergency physicians across Canada since the Canadian Medical Directory lists 99% of all practicing physicians in Canada. No other national database contains postal addresses for Canadian emergency physicians.

Our study has some limitations. Despite using these rigorous methods, we obtained a relatively modest response rate of 38.2%; however, this is higher than other recent surveys among emergency physicians.[12,13] The response rate may be attributed to several factors such as influence from the COVID-19 pandemic, which is known to contribute increased burden and stress on Canadian emergency departments, resulting in less time and perhaps less interest for emergency physicians to complete surveys. Additionally, there was an increased hesitancy among the general population with touching foreign materials, including mail, in fear of virus transmission. The survey was conducted from June 2021 to December 2021, in the midst of the pandemic. Furthermore, the Canadian Medical Directory is a common source for other postal surveys; thus, there is a possibility of overlap with other studies. Physicians who receive multiple consecutive surveys may find this too overwhelming and may be less likely to respond.

Our study contributes to an important and labour-intensive aspect of the methodology of postal surveys. Future studies should continue to study the effects of personalization using our methods and include hand-written or e-signed salutations compared to hand-written or e-signed generic salutations to determine if this would enhance response rates.

5.6 Conclusion

There was no significant difference in physician response rate between hand-signed and e-signed cover letter and reminder letters. Electronic signatures should be used in future postal surveys among physicians to save on time and labour without impacting response rates.

5.7 Tables and Figures

Figure 5.1 Participants and Response Rate in Hand-Signature Group versus Electronic-Signed Group

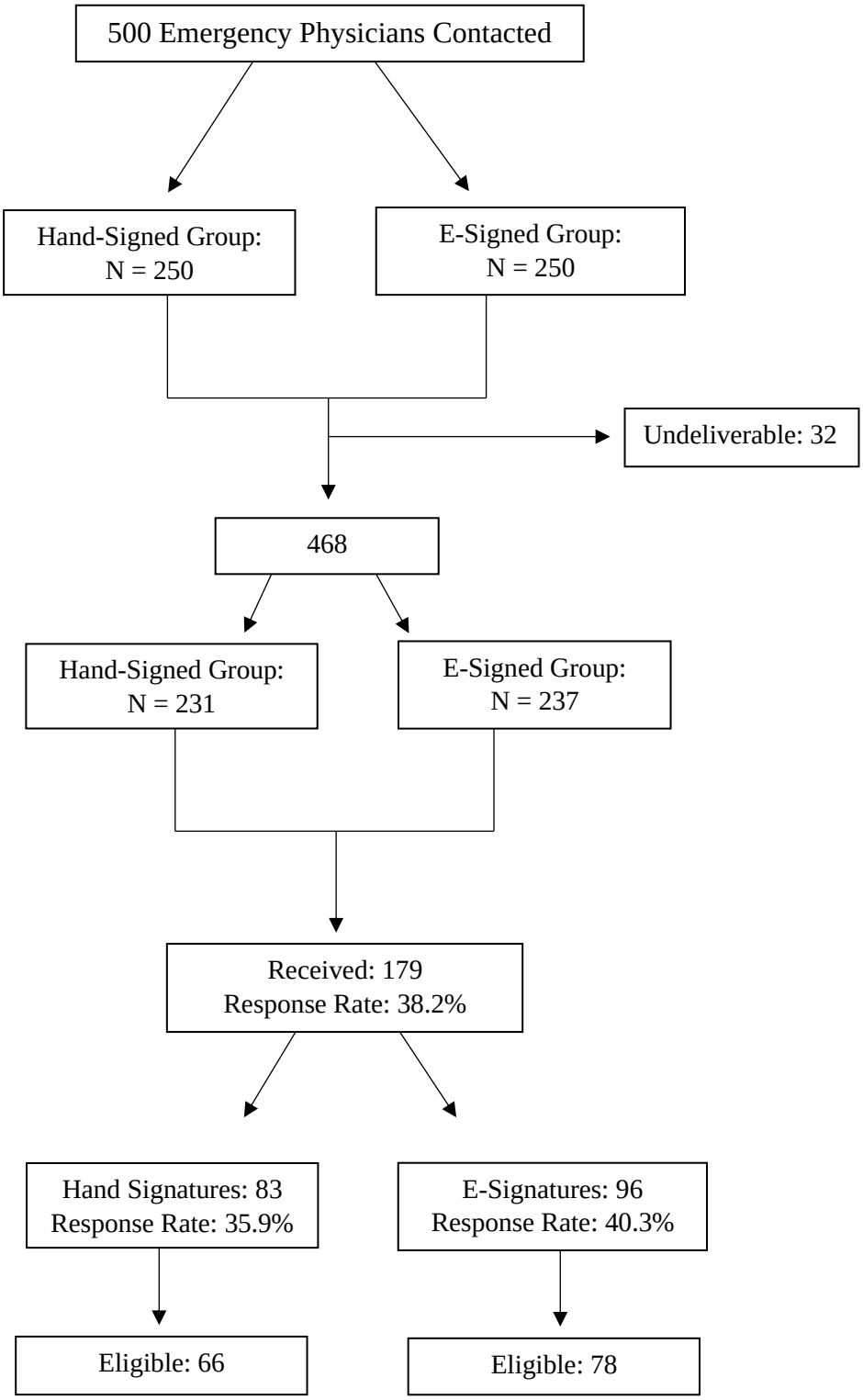

Table 5.1 Demographics and Practice Setting among Hand-Signature and Electronic-Signature Groups and Eligible Emergency Physicians

Characteristic	Hand-Signature N (%)	Electronic-Signature N (%)
Gender	**N=66**	**N=78**
Female	27 (40.9)	24 (30.8)
Male	39 (59.1)	53 (67.9)
Other	0 (0)	0 (0)
Prefer not to say	0 (0)	1 (1.3)
Language†	**N=83**	**N=96**
English	68 (81.9)	79 (82.3)
French	15 (18.1)	17 (17.7)
Years of practice	**N=66**	**N=78**
1-4	3 (4.5)	2 (2.6)
5-9	11 (16.7)	12 (15.4)
10-19	26 (39.4)	32 (41.0)
≥ 20	26 (39.4)	32 (41.0)
Region*	**N=83**	**N=96**
Western Canada	23 (27.7)	35 (36.5)
Ontario	33 (39.8)	39 (40.6)
Quebec	19 (22.9)	16 (16.7)
Eastern Canada	8 (9.6)	6 (6.3)
Canadian professional designation**	**N=66**	**N=78**
CCFP	1 (1.5)	2 (2.6)
CCFP-EM	33 (50.0)	40 (51.3)
FRCPC-EM	16 (24.2)	20 (25.6)
Multiple	16 (24.2)	13 (16.7)
Other	0 (0)	3 (3.8)
Practice setting	**N=68**	**N=78**
Academic Health Centre	21 (30.9)	23 (29.5)
Community/District General Hospital: Teaching	35 (51.5)	40 (51.3)
Community/District General Hospital: Non-Teaching	9 (13.2)	9 (11.5)
Rural	3 (4.4)	6 (7.7)
Other	0 (0)	2 (2.6)
Patient visits to ED per year	**N=65**	**N=77**
< 30,000	12 (18.5)	7 (9.1)
30,000 – 59,999	17 (26.2)	25 (32.5)
60,000 – 79,999	21 (32.3)	23 (29.9)
> 80,000	15 (23.1)	22 (28.6)

*Region and †Language preference : for all respondents, regardless of eligibility

*Region: Western Canada: British Columbia, Alberta, Saskatchewan
Eastern Canada: Prince Edward Island, Nova Scotia, Newfoundland & Labrador, New Brunswick

**CCFP: Canadian College of Family Physicians; CCFP-EM: CCFP with a specialization in Emergency Medicine; FRCPC-EM: Fellow of the Royal College of Physicians and Surgeons of Canada in Emergency Medicine

Table 5.2 Response Rates in Hand-Signed versus E-Signed Groups Overall and Stratified by Language Preference

Language preference	Hand-Signed	E-Signed	Absolute Difference (95% CI)	*P**	Interaction Test, *P***
Overall	35.9%	40.3%	-4.6% (-13.4% to 4.2%)	0.31	0.61
English	34%	39.3%	-5.3% (-14.7% to 4.1%)	0.27	
French	48.4%	47.2%	1.2% (-22.8% to 25.2%)	0.92	

*Obtained from chi-square test

**Obtained from logistic regression analysis including an interaction between signature type and language preference

5.8 References

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Chapter 6: Discussion

This chapter includes an overall summary of the main findings from this thesis and a discussion on its strengths and limitations as well as important considerations and implications for future research in the area of headache management in the emergency department.

6.1 Overview

This manuscript-based thesis described the effectiveness of the sphenopalatine ganglion (SPG) block for the treatment of primary headache disorders in the emergency department (ED). In Chapter 2, we described the classification, epidemiology and physiology of primary headache disorders. We reviewed current recommended treatment options for primary headaches in the ED and summarized the diversity and suboptimal profiles of these pharmacotherapies. We also described treatment alternatives, known as peripheral nerve blocks (PNBs), including the SPG block, with respect to anatomy and their mechanism of action. In Chapter 3, we conducted a systematic review and meta-analysis of existing trials to study the effectiveness of PNBs for the treatment of primary headache disorders. We investigated pain relief within 120 minutes as our primary outcome as well as other important outcomes including pain within 2 and 72 hours, adverse events, and any relapse of headache resulting in readmission to hospital. In Chapter 4, we reported on a national postal survey to determine current practice patterns for primary headache disorders in Canada and emergency physician perspectives towards PNBs. In Chapter 5, we presented findings from a randomized controlled trial, embedded as a sub-study within our postal survey described in Chapter 4, providing useful insights into methodology of future postal surveys.

6.2 Key Findings

We generated three manuscripts from this thesis. The first examined the effectiveness of the SPG block for treating primary headache disorders, while the second helped to inform

important design features of a future trial to further study the comparative effectiveness of the SPG block versus standard treatment. The third manuscript was an embedded study within a trial comparing two different methods of notification in a postal survey. The first manuscript reported a systematic review and meta-analysis with the following key findings: i) PNBs including the occipital nerve block and SPG block are effective for rapid pain relief when compared to placebo at 1, 5, 15 and 30 minutes; ii) the SPG block is the safest and least invasive procedure, especially using intranasal droplets of lidocaine; iii) PNBs are not associated with any serious adverse events; iv) there is significant heterogeneity in existing trials and insufficient evidence to determine the effectiveness of PNBs compared to standard therapy; and v) a future trial is needed to compare the SPG block with standard therapy. The second reported on a national survey of Canadian emergency physicians to identify current practice patterns for primary headache disorders and to determine perspectives and attitudes towards PNBs. We found that intravenous (IV) non-steroidal anti-inflammatory drugs (NSAIDs) alone and dopamine antagonists with or without ketorolac were amongst the most commonly used pharmacotherapies for primary headaches in the ED and would be an ideal comparator against the SPG block in a future trial. This finding conforms with guidelines and recommendations from the Canadian Headache Society, which lists similar pharmacotherapies as first-line treatment options for primary headache in the ED and shows current ED physicians comply with these standards. We also found PNBs are not being performed by a large proportion of emergency physicians and the SPG block is the least commonly practiced procedure amongst experienced physicians. Physicians have positive acceptability towards PNBs and would consider using them as a first-line alternative, given sufficient evidence from a randomized controlled trial.

Our survey will be used to inform the design of a future randomized controlled trial. First, it provided information about physicians' perceptions of the clinically important time to reassess headache pain, which is at 30 and 60 minutes. Second, it identified an improvement in 3 to 4 points on a 10-point scale as clinically significant for most physicians. Third, it indicated that most physicians would be open to enrolling their patients with primary headache into a future trial. Our last study was a randomized controlled trial embedded within the survey described in Chapter 4. We conducted this trial to improve methods for future postal surveys by comparing the effect of hand signature versus electronic signature on response rate. Although hand-signatures are more authentic and may carry over to a sense of trust, we found there was no significant difference in response rate between the two groups and this step should be replaced with electronic signatures to save time, labour and costs associated with future postal surveys.

6.3 Previous Studies

Current research with regards to the SPG block is limited and the Canadian Headache society recommends intranasal lidocaine with weak, low-quality evidence.[1] Additionally, the American Headache Society lists intranasal lidocaine as Level C (possibly effective for acute migraine based on available evidence).[2,3] Thus, the SPG block cannot be recommended with confidence as an effective alternative treatment method for emergency physicians. Several systematic reviews have been conducted studying the effects of the SPG block for specific primary headache disorders[4,5]; however, none of these studies performed a meta-analysis which show trends of effectiveness over time. Our study is unique in that we found evidence for pain relief for PNBs, including the SPG block, compared to placebo, at 1, 5, 15 and 30 minutes.[6] Given the ease of use, we were able to provide strong evidence to recommend the SPG block as an adjunct therapy for primary headache disorders in the ED.

With regards to current recommendations for primary headache disorders in the ED, the Canadian Headache Society strongly recommends dopamine antagonists (prochlorperazine, metoclopramide), triptans (i.e. sumatriptan) and intravenous (IV) non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. ketorolac) for acute migraine in the ED.[1] Due to the diversity of available pharmacotherapies, it was unclear if current practicing ED physicians comply to these standards. Our national survey found current ED physicians conform to these standards; medications used in high frequency were dopamine antagonists, NSAIDs alone and in combination with a dopamine antagonist and acetaminophen. Existing literature suggests parenteral opioids are overused in the management of primary headache disorders in the ED.[7–10] Among our sample of emergency physicians, we found opioid use was very seldom used in high frequency for primary headache. To the best of our knowledge, it was unknown as to whether PNBs are routinely used for primary headache and at which frequency, among Canadian emergency physicians. Current perspectives and attitudes towards PNBs were also unknown. Our national survey adds to this understudied area of research. We discovered ED physicians generally have positive acceptability towards PNBs such that they deem these procedures as safe, effective, are comfortable using these procedures and would consider them as a first-line treatment given sufficient evidence from a future trial.

6.4 Strengths and Limitations

This thesis has several strengths. In our first study, we conducted a thorough systematic review and meta-analysis using a rigorous search strategy and adhered to robust and well-established guidelines for reporting our outcomes. To the best of our knowledge, this was the first systematic review and meta-analysis to group clinically relevant PNBs, including the occipital nerve block, SPG block and trigger point injections together to study their effectiveness for primary headache disorders in general. Our search criteria were broad to include any comparator,

such as placebo or active therapy. This allowed us to conduct a meta-analysis of studies comparing PNBs against placebo separately to active therapy. Our main outcome was pain within 120 minutes; this is a broad range of time points which are clinically relevant for emergency physicians and allowed us to organize our meta-analysis by common time points of pain assessment from existing trials. This study had some limitations, including clinical heterogeneity. We found no trials which studied trigger point injections and we grouped occipital nerve blocks and SPG blocks together; although these are both types of PNBs, their mechanism of action is different as they act on different target locations of the head. Furthermore, the type of anesthetic used across studies varied between lidocaine and bupivacaine and the dose of anesthetic was different, ranging from 1.5 mg to 80 mg. Despite this heterogeneity, we believe a meta-analysis was appropriate since grouping these studies allowed us to make conclusions about the effectiveness of PNBs for primary headache in general. Another limitation with our systematic review and meta-analysis was found in our quality assessment, where three studies were rated as high risk of bias arising from either the randomization process or in selection of the reported result; however, we conducted a sensitivity analysis excluding studies deemed high risk of bias and found no significant difference in treatment effect. Additionally, there was a mix of studies included in the ED and clinic setting; to determine if our results can be generalized to the ED population, we conducted a sensitivity analysis and found no significant difference.

Our national survey had several strengths. The survey questionnaire underwent stringent refinement according to the methodology of previous well-established postal surveys.[11,12] The survey questionnaire went through several iterations of modifications with input from experienced emergency physicians at The Ottawa Hospital, before being finalized. We also performed cognitive interviews with 10 emergency physicians in both English and French to ensure our

survey was comprehensive. Cognitive interviews have been used previously and are a useful method to identify any confusion by using non-verbal cues for hesitancy, such as facial expressions. Our survey was carefully designed, with considerations towards designing a future trial. The primary limitation of this thesis was the relatively modest response rate obtained from our national postal survey. Despite using rigorous methods from previous postal surveys, our response rate was lower than expected and thus, our results may be vulnerable to an increased risk of non-response bias. We suspect the primary reason for a lower-than-expected response rate was the COVID-19 pandemic, which is known to have cause increased stress and burden on Canadian EDs and hesitancy towards touching foreign materials including mail, which may be attributable to virus transmission. With regards to our modest response rate, we compared characteristics of respondents and non-respondents and found no statistically significant differences with respect to geographical region and language preference.

Another limitation of this thesis is that we did not mention other PNBs in our comparison against SPG blocks, namely the supraorbital, infraorbital, and supratrochlear nerve blocks. Some emergency physicians in our survey expressed interest in these PNBs. The main reason for not mentioning these PNBs is due to the limited evidence from randomized controlled trials to support their use. These other PNBs are more invasive procedures of the face, around the orbital region to block the supraorbital, infraorbital, or supratrochlear nerves and alleviate headache pain. We chose the main PNBs a priori which have been reported as effective for alleviating headache pain and are easier to perform compared to other PNBs.

Finally, we did not study the acceptability and preference among adult patients with primary headache disorders. Patient preference towards their treatment is an important consideration. Further investigation is needed to determine which method of treatment patients

prefer and if patients would accept intranasal droplets of an anesthetic compared to IV treatment options.

6.5 Clinical Implications

Findings from this research has several clinical implications. Primarily, we found the SPG block is effective for rapid pain relief compared to placebo.[6] Thus, emergency physicians are encouraged to use findings from our systematic-review and meta-analysis to use the SPG block as an adjunct therapy to achieve rapid pain relief associated with primary headache disorders in the ED. The SPG block is the simplest and least invasive method, especially using techniques such as the Method of Barre (i.e. intranasal droplets of lidocaine).[13,14]

The optimal treatment of primary headache disorders in the ED remains an important area of research due to its high prevalence and cause of significant disability. Current recommended pharmacotherapies are suboptimal, where effective pain relief usually takes up to 60 minutes and associated with side effects (Chapter 2). Most current treatment options are oral or IV; however oral administration is not tolerated when there is associated nausea and vomiting. The SPG block bypasses the oral and gastrointestinal route and IV routes, where needlestick injuries are more common, with a simple intranasal route. This thesis supports the use of the SPG block; however, further research is needed in the form of a multi-centre randomized controlled trial to study its comparative effectiveness with standard treatments in order to support its use as a first-line treatment option.

6.6 Research Implications and Next Steps

Findings from this thesis lay the groundwork for a future multi-centre trial to study the effectiveness of the SPG block. We gained a comprehensive understanding of existing trials with respect to their drawbacks and surveyed practicing emergency physicians across Canada to

determine detailed aspects of a future trial including insight towards the minimal clinically important difference, required for sample size calculations to power this trial.

6.7 Conclusion

This thesis provides evidence that the SPG block is effective for rapid pain relief compared to placebo. Our findings suggest the SPG block can be used as an adjunct therapy with current recommend treatment options for faster relief of primary headache pain in the ED. We determined that the SPG block is the least utilized procedure among Canadian emergency physicians despite the ease of use and rapidity of intranasal droplets of lidocaine. Increased awareness of this procedure and continued training on headache management for emergency physicians is important to ensure faster and more effective treatment options for patients with primary headache in the ED. Future research is needed in the form of a multi-centre randomized controlled trial before the SPG block can be recommended as a first-line alternative.

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