Understanding and Improving Pharmacological Delirium Prevention in Critically Ill Trauma Patients

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Preface

This is an article-based thesis composed of three major chapters and two component articles. The primary author, Ms. Gabriele Zitikyte, was responsible for conceptualization, design, analysis, and primary manuscript drafting for the entirety of the content. Ms. Zitikyte takes responsibility for the integrity of the data and the accuracy of the analysis. The roles of the other individual co-authors are listed within each component article.

Ethics approval was required and obtained for one component of this thesis. The Ottawa Health Science Network Research Ethics Board approval for the health records review presented in Chapter 4 is included in Appendix B.

Thesis Abstract

Background: Delirium is common in critically ill trauma patients, yet there is no evidence-based standard of care sedation agent for this population.

Objective: This thesis aims to expand knowledge around dexmedetomidine, a sedative that has demonstrated potential superiority in other clinical patient populations.

Methods: We conducted a systematic review and network meta-analysis to compare the effectiveness of sedatives on delirium and associated patient outcomes. We conducted a health records review of sedated trauma patients at The Ottawa Hospital. We derived a simple mathematical model to demonstrate potential impact of dexmedetomidine on resources.

Results: There was no statistical difference between sedatives in preventing delirium. Approximately 79% of critical trauma patients were sedated with propofol, 18% with propofol and dexmedetomidine, and 3 with dexmedetomidine. Increasing the proportion of patients receiving propofol with adjunct dexmedetomidine could improve the number of freed ICU bed-days.

Conclusion: Dexmedetomidine could have potential benefits in improving outcomes for critically ill trauma patients.

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Glossary

APACHE – Acute Physiology and Chronic Health Evaluation

CAM-ICU – Confusion Assessment Method for the Intensive Care Unit

CrI – Credible Interval

FE – Fixed effects

GRADE – Grading of Recommendations, Assessment, Development and Evaluations

HR – Hazard Ratio

ICDSC – Intensive Care Delirium Screening Checklist

ICU – Intensive Care Unit

IQR – Interquartile Range

LOS – Length of Stay

MD – Mean Difference

NMA – Network Meta-Analysis

PADIS – Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption

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

RCT – Randomized Controlled Trial

RE – Random Effects

RoB2 – Risk of Bias tool v.2

SCCM – Society of Critical Care Medicine

SUCRA – Surface Under the Cumulative Ranking score

CHAPTER ONE: INTRODUCTION

1.1 Primary Research Objectives:

The primary objective of this thesis is to improve the understanding of delirium in critically ill trauma patients, including its epidemiology, modifiable risk factors, and impact on hospital resources. Specifically, in this thesis work we:

1) Systematically reviewed the literature to compare the effect of different sedatives on delirium incidence.
2) Perform a retrospective health records review to understand current sedation practice at The Ottawa Hospital
3) Derive a simple mathematical model to predict length of stay in the intensive care unit based on sedative choice and corresponding delirium risk

1.2 Overview of Chapters

Chapter 2 – Background

This introductory chapter summarizes the current understanding of the relationship between sedatives and delirium in trauma patients. We will discuss the prevalence, risk factors, and related outcomes of delirium, as well as the contributions from and comparisons between different sedatives in its development.

Chapter 3 – Systematic review and network meta-analysis

This chapter addresses the question: "Is dexmedetomidine superior to other pharmacological strategies in preventing delirium?". The paper is titled "Pharmacological Interventions to Prevent Delirium in Trauma Patients: A systematic review and network meta-

analysis of randomized controlled trials", and has been accepted for publication in Critical Care Explorations (CCE).

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Chapter 4 – Health records review and mathematical model

This chapter uses data retrieved through the electronic medical records administrative database at The Ottawa Hospital, Civic Campus, to address the questions: "What are the current sedation practices for critically ill trauma patients?" and "What is the impact of supplementing propofol sedation with dexmedetomidine on ICU capacity?". This manuscript is currently being prepared for submission.

Chapter 5 – Discussion

This final chapter summarizes the key findings and clinical importance of this thesis and outlines future directions for research on this topic.

CHAPTER TWO: BACKGROUND

2.1 Preface

This background chapter will focus primarily on the epidemiology of delirium, why dexmedetomidine may play an important role in its prevention in trauma patients, and why it is important for more research to focus on the trauma subgroup of intensive care unit (ICU) populations. This review did not require ethics approval.

2.2 Introduction

2.2.1 Background

Delirium is characterized by a disturbance of consciousness with inattention and acute change in cognition, which is not better accounted for by a pre-existing or evolving illness.(1) In the ICU setting, it is diagnosed using either the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC).(2–4)

Delirium is reported in 60-80% of critically ill patients receiving mechanical ventilation, yet evidence suggests that delirium may be preventable in 30% to 40% of cases.(5) It is associated with increased morbidity, mortality, length of stay, and patient care costs.(1,6–8) In the United States alone, it leads to tens of millions of additional inpatient days annually and billions of dollars spent.(5,6,9) At a patient level, the ICU costs associated with those who develop delirium is almost $4000 USD more than those who do not.(10)

With unprecedented capacity shortages in hospitals, mitigating delirium would not only benefit patients but it would also have important implications for cost reduction and improved resource use efficiency.(11)

2.2.2 Risk Factors

There are many risk factors for delirium in critically ill patients. Based on sixty-eight studies, benzodiazepine use, older age, increased Acute Physiology and Chronic Health Evaluation (APACHE), and pre-ICU trauma are among risk factors with strong evidence indicating their association with delirium.(4) Among sedatives, propofol or dexmedetomidine are preferable to benzodiazepines because of decreased rates of delirium and decreased duration of mechanical ventilation and ICU LOS.(4)

2.2.3 Trauma Patients

Delirium is more common in critically ill trauma patients than in their non-trauma counterparts, yet predicting the occurrence of delirium in trauma patients is more difficult.(8,12) Like the general ICU population, there are many modifiable and non-modifiable risk factors that can contribute to acute cognitive impairment. Trauma patients are, however, additionally hindered because their patient characteristics are inherently different from the general ICU patients most prediction models are based on. Trauma patients tend to be younger, often present with highly acute pain, and/or traumatic brain injury (TBI).(1) Yet, treatment and management are based predominantly on extrapolated concepts from other patient populations. The 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) that is used to guide practice in trauma patients is based on studies of generalized ICU populations.(4) Important risk factors that are prevalent in trauma patients, including positive blood alcohol concentration (BAC) and TBI at admission, were not considered nor included in the development of the validated PRE-DELIRIC model for intensive care patients.(13)

Not only prediction, but diagnosis of delirium in trauma patients is also problematic.(12) Hyperactive delirium is easier to detect than hypoactive, which is troublesome for the trauma population that is commonly heavily sedated or confounded by the presence of concurrent TBI.(12) Even with validated methods such as the CAM-ICU, delirium remains severely under-diagnosed, under-documented, and under-treated in up to 84% of ICU patients.(12)

2.2.4 Previous research

One of the first assessments of delirium in trauma patients was a case-control study by Blondell et al. This study assessed 265 adult (>18 years) trauma patients who were admitted to a

level 1 trauma center. Of these cases, 120 were discharged with a diagnosis of delirium or a delirium-related disorder and 145 were used as non-delirious controls. Adjusted regression found that older age (>45 years) and a positive blood alcohol concentration at admission were significantly associated with the development of delirium.(1)

A 2017 prospective, observational study by Von Rueden et al looked at 215 adult (>18 years) trauma patients across three large, urban trauma centers. The study excluded patients with TBI and was limited in its assessment of relatively mild trauma cases where patients had a Glasgow coma score no less than 8. Von Rueden et al concluded that use of sedatives, analgesics, mechanical ventilation, increased injury severity, positive toxicology screen, and elevated blood alcohol levels were all significantly associated with delirium in trauma patients.(6)

Similarly, a 2019 prospective observational study by Duceppe et al assessed 150 adult (>18 years) trauma patients across two level 1 trauma ICU centers. Approximately 40% of patients screened positive for delirium during their ICU stay using the validated CAM-ICU method. An unadjusted analysis in the study found older age, higher injury severity, and TBI to be significantly associated with delirium.(14)

2.2.5 Dexmedetomidine

Given the consistent evidence for the association between TBI, positive BAC, and opioids on the development of delirium in ICU trauma patients, alpha-2 adrenergic receptor agonists have emerged at the forefront of recent studies on delirium in trauma patients.(15,16)

Alpha-2 adrenergic receptor agonists exert their properties via inhibition of norepinephrine release from presynaptic neuron, centrally induced sedation at the locus coeruleus, and centrally mediated pain modification at the dorsal horn.(15,16) In other words,

they are able to produce sedation, analgesia, and partially block acute withdrawal symptoms in chronic opioid and alcohol users.(16) Dexmedetomidine (Precedex), a very highly selective alpha-2 agonist, is most commonly used for clinical sedation.(16) Its side effects include hypotension and bradycardia due to its loss of selectivity as dosage is increased by intravenous (IV) bolus injection or rapid infusion.(16) This may lead to an initial increase in blood pressure and drop in heart rate, but normalizes within 15 minutes.(16)

A major advantage of dexmedetomidine over other sedatives is that it has a minimal effect on the respiratory system.(16) It allows for sedation without causing respiratory depression or requiring mechanical ventilation.(16) Additionally, its analgesic effects allow for a reduction in opioid requirements by 50-75% when used concurrently.(16,18) Its euphoric, calming effects coupled with decreased opioid and mechanical ventilation requirements makes dexmedetomidine a promising sedative with strong preventative properties against delirium, especially in the context of concurrent painful injuries.(16)

Currently, no pharmacologic agents have demonstrated sufficient efficacy for the primary prevention of delirium. When patients require sedation, the PADIS guidelines found that dexmedetomidine was associated with lower delirium incidence in each study assessed when compared to other agents, other outcomes that they deemed critical did not show any significant results favouring the alpha-2 agonist.(4) For sedation, the PADIS guidelines noted that incorporating both propofol and dexmedetomidine into practice was likely acceptable and feasible.(4) The team issued a conditional recommendation to use either agent for sedation of critically ill adults, but noted that larger, well-conducted studies are needed to assess critical outcomes between the two. However, these practice-guiding recommendations are based on studies of post-operative, non-trauma patients.(4)

2.3 Conclusion

Most delirium studies focus on elderly medical patients or those undergoing cardiac surgery. Relatively little attention has been given to the trauma population.(1,12,19) This knowledge gap is vital to explore due to the heterogenous demographics, hypoactive presentation of delirium, and additional risk factors that must be considered. Dexmedetomidine may be a promising pharmacological intervention with benefits to patients by minimizing respiratory depression, minimizing opioid needs, and decreasing hospital and ICU length of stay; and, benefitting the healthcare system by increased ICU capacity and decreased medical costs. Through two main articles, this thesis aims to explore the impact of dexmedetomidine on delirium and ICU capacity within the critically ill trauma population.

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CHAPTER THREE: Pharmacological Interventions to Prevent Delirium in Trauma Patients: A systematic review and network meta-analysis of randomized controlled trials

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Appendix: Submission confirmation of Chapter 3:

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3.1 Preface

This chapter is a systematic review and network meta-analysis examining the comparative effectiveness of pharmacological interventions on delirium incidence in critically ill trauma patients. This study did not require ethics approval. A confirmation of acceptance is available in the Appendix.

3.2 Abstract

Objective: To compare the relative efficacy of pharmacologic interventions in the prevention of delirium in ICU trauma patients.

Methods: We searched MEDLINE, Embase, and Cochrane Registry of Clinical Trials from database inception until June 7, 2022. We included randomized controlled trials comparing pharmacologic interventions in critically ill trauma patients. Two reviewers independently screened studies for eligibility, extracted data, and assessed risk of bias. PRISMA guidelines for network analysis were followed. Random-effects models were fit using a Bayesian approach to network meta-analysis. Between-group comparisons were estimated using hazard ratios (HR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, each with 95% credible intervals (95% CrIs). Treatment rankings were estimated for each outcome in the form of surface under the cumulative ranking curve (SUCRA) values

Data Synthesis: A total 3541 citations were screened; 6 randomized clinical trials (n = 382 patients) were included. Compared to combined propofol-dexmedetomidine, there may be no difference in delirium incidence with dexmedetomidine (HR 1.44, 95% CrI 0.39-6.94), propofol (HR 2.38, 95% CrI 0.68-11.36), nor haloperidol (HR 3.38, 95% CrI 0.65-21.79); and, compared to dexmedetomidine alone, there may be no effect with propofol (HR 1.66, 95% CrI 0.79, 3.69) nor haloperidol (HR 2.30, 95% CrI 0.88-6.61).

Conclusions: The results of this network meta-analysis suggest that there is no difference found between pharmacological interventions on delirium occurrence, length of ICU stay, length of hospital stay, or mortality, in trauma ICU patients.

3.3 Introduction

3.3.1 Background

Delirium is characterized as an acute change in mental status, accompanied by inattention, disorganized thinking, and/or an altered level of consciousness.(1–3) The development of delirium is associated with both patient-important and system-important adverse outcomes such as increased mortality, prolonged mechanical ventilation, prolonged hospitalization, and increased treatment costs.(4–8) The 2018 Society of Critical Care (SCCM) guidelines suggest against use of pharmacologic treatment for delirium, based on very low to low quality of evidence.(9) The trials assessed by the SCCM consistently showed that pharmacologic interventions (ie. haloperidol, dexmedetomidine) resulted in a lower incidence of delirium, compared to non-pharmacological treatments, but none reported a clinically important nor statistically significant difference for any of the other outcomes that the study authors deemed critical.(9) Recently, a 2021 network meta-analysis by Burry et al. assessed 11 different pharmacological interventions for the prevention of delirium in mixed medical-surgical critical care patients.(10) They compared dexmedetomidine to benzodiazepines, propofol, antipsychotics, melatonin, opioids, or a combination of these drugs and concluded it probably reduces delirium occurrence and length of intensive care unit (ICU) stay.(10) Similarly, a 2022 meta-analysis conducted by Lewis et al. concluded that compared to other sedatives, dexmedetomidine was associated with a lower incidence of delirium among older critically ill adults.(11)

While several studies have assessed pharmacological interventions for the prevention of delirium in critically ill patients, not all have been compared in the trauma subgroup whose demographic and clinical characteristics are inherently different. Additionally, the few studies

that have focused on this population yield very small sample sizes and are severely underpowered.(12,13) Thus, by combining the results, a network meta-analysis may facilitate stronger conclusions in this unique population.

Trauma patients tend to be younger than the average patient admitted to the ICU, and are more frequently male.(14,15) These patients may have severe brain injuries, for which delirium prevalence can be as high as 90%.(16) Dexmedetomidine has become increasingly popular for use in neurocritical patients, where management is especially challenging and current agents come under scrutiny.(17) There are significant concerns around long-term use of propofol, a first-line sedative for trauma patients, and dexmedetomidine could be a reasonable alternative.(18) Additionally, trauma patients are more commonly affected by acute rather than chronic physiologic derangements, often have no previous history of cognitive dysfunction, and are often co-managed with significant pain medications.(19,20) Dexmedetomidine may demonstrate an advantage in trauma patients given it is a highly selective alpha-2-adrenergic receptor (α2-AR) agonist that specifically targets the locus coeruleus of the brain stem and the spinal cord, which are respectively the principal sites for sedative and analgesic action.(21) Also, a 2012 systematic review found that postoperative opioid use decreased by 30% within the first 24 hours when dexmedetomidine was used.(22) This is an important consideration for trauma patients given their significant pain burden compared to general ICU patients and associated adverse events, including greater than average risk of developing opioid use disorder after discharge.(23,24)

Whether any type of prophylaxis is effective is unclear but, given the abundance of pharmaceuticals available, we believe it is important to synthesize the available evidence for this distinct and high risk trauma population to further supplement bedside decision

making.(4,10,15,16,25) Our primary objective was to synthesize available evidence from randomized controlled trials (RCTs) that examined pharmacologic interventions for prevention of delirium in adult trauma patients (≥ 16 years old) who were admitted to the ICU and required sedation. The primary outcome was incidence of delirium; secondary outcomes were length of ICU stay, length of hospital stay, and hospital mortality.

3.4 Methods

We registered this review prospectively with the Center for Open Science.(26) The completed review has been prepared in conformance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Extension Statement for Network Meta-analysis.(27)

3.4.1 Literature Search

The search strategy was developed with a librarian experienced in systematic reviews (Supplementary Table 1). We utilized the following databases: MEDLINE, Embase, and Cochrane Registry of Clinical Trials, and included articles from database inception until June 7, 2022.

We included RCTs that examined pharmacologic interventions in adult trauma patients (≥ 16 years old) who were admitted to the ICU and required or were anticipated to require sedation at randomization. Studies were required to report on at least one of: delirium occurrence, length of ICU stay, length of hospital stay, or hospital mortality. The selection of outcomes was informed by the core outcome set for research evaluating interventions to prevent and/or treat delirium in critically ill adults.(22) We did not exclude trials based on comparator/control group, mechanism of injury (blunt vs penetrating), anatomic injury (head

injury vs other), or study population (civilian vs military). We only included full-text studies in the English language.

3.4.2 Article Selection

Two reviewers (GZ, DCR) independently screened search results in two phases using Covidence Systematic Review Software; the first comprised title and abstract screening only. A pilot exercise was conducted to ensure consistency between reviewers. Eligible studies proceeded to the second phase where full texts were evaluated for completeness and content. Discrepancies in either phase were resolved by consensus discussion between reviewers.

3.4.3 Data Extraction

A standardized data extraction form was created and piloted a priori. We extracted data on study characteristics (journal name, publication year, authors, country of origin), participant characteristics (age, sex, follow-up period), intervention and comparator details (medication name, dose), and outcome data (delirium incidence [yes/no], length of ICU stay [days], length of hospital stay [days], and mortality [yes/no]). We defined delirium as a positive score on the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) score, and only included deaths that occurred up to hospital discharge.

3.4.4 Risk of Bias Assessment

We assessed risk of bias using the Cochrane Risk of Bias tool for randomized trials version 2 (RoB2).(23) Overall risk of bias was judged across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. The domains were judged using high, some

concerns, or low risk of bias judgment. The effect of interest that was used for the RoB2 assessment was the effect of assignment to the intervention at baseline.

3.4.5 Statistical Analysis

A NMA was performed and we evaluated the certainty of the evidence from the NMA following Cochrane's approach for assessing underlying assumptions.(24) We addressed transitivity by appraising the clinical and methodologic characteristics of the included studies. We also conducted fixed effects (FE) pairwise meta-analyses to evaluate statistical heterogeneity of treatment effects using I^2 values.

We performed NMA on interventions that connected to an evidence network. All NMAs were evaluated under a Bayesian framework with Markov Chain Monte Carlo Simulation, using BUGSnet 1.0.4 in RStudio Desktop 1.4.1717. Dichotomous outcomes were modelled using binomial family and clog-log link function to account for differences in follow-up time and obtain hazard ratios (HRs) with 95% credible intervals (95% CrI). Continuous outcomes were modelled using normal family and identity link to obtain mean differences with 95% CrI. We ran the model simulations with a burn-in of 25,000 iterations and a sampling of 50,000 iterations from 3 chains of initial values.

Adequacy of model fit was evaluated by comparing the posterior total residual deviance within the number of unconstrained data points. We fit fixed and random effects models for each outcome; the selection between models was based on deviance information criteria (DIC). Smaller DIC values indicated a greater fit, with a difference greater than five points suggesting an important difference. Model convergence was visually inspected using trace plots and Gelman-Rubin diagnostics. Inconsistency was evaluated by comparing DIC values with those

from the corresponding consistency model. Treatment rankings were estimated for each outcome in the form of surface under the cumulative ranking curve (SUCRA) values.(24)

3.5 Results

Among a total of 3,541 citations screened, six trials met the eligibility criteria (Figure 1): two studies compared propofol and dexmedetomidine (n=117), two compared midazolam and propofol (n=163), one compared propofol and morphine (n=42), and one compared dexmedetomidine and haloperidol (n=60). Reviewers had a final measured agreement of 99.7%. In total, we analyzed data from 382 individuals: 134 received propofol, 78 received dexmedetomidine, 66 received midazolam, 33 received midazolam combined with propofol, 30 received haloperidol, 20 received dexmedetomidine combined with propofol, and 19 received morphine.

Key features of all studies are presented in Table 1. The mean ages of participants were balanced across all studies. Trials were geographically dispersed between the United States (33%), Spain (33%), Egypt (17%), and Iran (17%). Inclusion criteria were comparable across studies. All studies enrolled adult (≥ 16 years old) trauma patients upon admission to the ICU, and patients required sedation at randomization. The effect of induction of sedation was not assessed as patient randomization and evaluation began after the initial stabilization period, including emergency room admittance, radiograph assessment, and surgery, if indicated.(25) All trials that assessed incidence of delirium used the same validated delirium assessment tool: Confusion Assessment Method for the ICU (CAM-ICU).

All but one study had a low risk of bias across all RoB2 domains (Supplementary Figure 1). Winings et al. had some concerns for risk of bias due to the lack of allocation sequence

concealment. However, baseline differences between intervention groups suggested no problem with the randomization process (Table 1).

Comparisons of total posterior residual deviance with the number of unconstrained data points for all FE and RE NMAs suggested model fits were adequate. For all outcomes, comparisons of DIC values suggested no important difference between FE and RE consistency models. Therefore, results from FE models are presented for all analyses (Table 2). Comparisons of DIC suggested no violation of the consistency assumption. Details of model fit statistics and checks for inconsistency are provided in Table 2 in the supplement.

Primary Outcome: Incidence of Delirium

Four treatment regimens were studied in three trials (Figure 2). Fixed effects model measures and SUCRA values are displayed in Table 2 and Supplemental Materials Table 3, respectively. Compared to combined dexmedetomidine and propofol, we found there may be no effect with dexmedetomidine (HR 1.44, 95% CrI 0.39-6.94), propofol (HR 2.38, 95% CrI 0.68-11.36), or haloperidol (HR 3.38, 95% CrI 0.65-21.79). Compared to dexmedetomidine alone, we found there may be no effect with propofol (HR 1.66, 95% CrI 0.79, 3.69) nor haloperidol (HR 2.30, 95% CrI 0.88-6.61). Compared to propofol, we found there may be no effect with haloperidol (HR 1.39, 95% CrI 0.40-5.05). SUCRA rankings suggest as estimated probability of 69% that combined propofol and dexmedetomidine rank as the superior sedative choice.

Secondary Outcomes (ICU LOS, hospital LOS, and mortality)

Six treatment regimens were studied in five trials for ICU LOS; three regimens were studied in two trials for hospital LOS; and, six regimens were studied in four trials for mortality.

There was no difference between any of the treatment regimens for any outcomes (Table 2). We found there may be no effect on any of the outcomes between any interventions.

3.6 Discussion

In this systematic review and network meta-analysis of seven treatment regimens from six trials enrolling 382 trauma patients, we found no statistically significant difference in efficacy between any pharmacological intervention in preventing delirium or mortality, nor shortening ICU or hospital LOS, in the trauma population.

Existing evidence does not provide a robust guideline for pharmaceutical prevention of delirium in the trauma population nor the broader ICU population. Burry et al. found that dexmedetomidine may be effective in preventing delirium in critically ill patients, compared to benzodiazepines and placebo, but the evidence is very uncertain.(10) Our network meta-analysis is the first to focus solely on trauma patients and combines evidence from smaller, severely underpowered trials.(12) The results suggest that all studied interventions are equal based on the outcomes assessed.

According to currently available randomized, double-blind, placebo-controlled, multicentre studies, intravenous (IV) dexmedetomidine is effective as a primary sedative in initially intubated and mechanically ventilated ICU patients and in non-intubated patients prior to and/or during surgical and other procedures.(32) Although many benefits for dexmedetomidine exist, the sedative should be used cautiously in patients with hypotension or bradycardia as it may exacerbate these effects and possibly cause heart block and/or severe ventricular dysfunction.(32–34) Additionally, the SPICE III trial showed an association between dexmedetomidine and higher mortality rates in patients younger than 65 years old, when

compared to usual care (i.e. propofol, midazolam, or other sedatives).(35) This is important to note in trauma patients because they tend to be younger than general critically ill patient due to differences in mechanisms.(14) A large majority of trauma patients are victims of assault, motor vehicle accidents, or toxic effects of drugs, whereas general ICU patients mostly present due to comorbidities (e.g. cerebral infarction, cardiovascular disease, heart failure, chronic obstructive pulmonary disease). (36–38)

3.6.2 Clinical and Research Implications

Our results provide a focused comparison of currently available pharmacological interventions for the prevention of delirium in the trauma populations. Considerations for future research include assessing hemodynamic safety for use early into the clinical course when patients may be more at risk for hemodynamic liability. This may introduce an important area for evidence-based risk stratification to determine patients that would benefit from early intervention with, or conversion to, dexmedetomidine. Narrowing down the broad scope of prognostic factors to a validated set that are associated with future delirium could allow primary care teams to screen for and act earlier on high-risk patients.

3.6.3 Limitations

Limitations of this study include our ability to conduct comparisons with interventions such as propranolol, melatonin, quetiapine, and risperidone, due to lack of network structure. Several interventions were left unevaluated and will require further trials to be published to assess its relative efficacy and safety compared to the 7 interventions evaluated in this review. Second, we were limited in our inability to perform Grading of Recommendations, Assessment, Development and Evaluations (GRADE). All closed loops were informed by multi-arm trials, rendering all comparisons coherent by definition and inhibiting any assessments for

inconsistency. Next, publication bias is difficult to judge in a network meta-analysis due to the limited number of studies for each pairwise comparison.(39) Finally, rankings based on SUCRA values should be interpreted with caution as they may be misleading.(40) By definition SUCRA is an estimated quantity and, as with any estimate, holds a degree of variability.(39) SUCRA rankings only consider primary outcomes, ignoring potential secondary benefits or harms, have no certainty assessments associated with them (ie. rankings may arise from low or very low evidence), and small differences may be exaggerated due to the ordinal nature of rankings.(40) One can avoid misleading circumstances by interpreting rankings in the light of certainty and confidence in the results (ie. as supporting information to point estimates and credible intervals) and not basing inferences solely on probabilities.(39–41) There is risk of focusing interpretations from these rankings due to the weak network structure (i.e. low number of existing trials).(41) The rankings are largely influenced by point estimates which, as indicated by the wide credible intervals, are grossly uncertain.

3.6.4 Strengths

This study has several strengths, including its a priori registration and comprehensive search strategy that involved 3 databases. By performing a NMA, we were able to include and compare a broad range of interventions that otherwise could not be evaluated through pairwise comparisons. NMA is also unique in its ability to calculate probabilities of treatment rankings, which can provide some indication to potential trends in treatment efficacy. Lastly, unlike previous reviews, there was overall very low risk of bias amongst our included randomized trials.

3.7 Conclusions

This NMA found no statistically significant difference between pharmacological interventions for the prevention of delirium in the ICU trauma population. Dexmedetomidine may be a reasonable adjunct or alternate sedative in this population.

Acknowledgments

We thank Risa Shorr, MLS (The Ottawa Hospital) for developing the electronic search strategies.

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3.9 Figures and Tables

Figure 1. PRISMA Flow Diagram

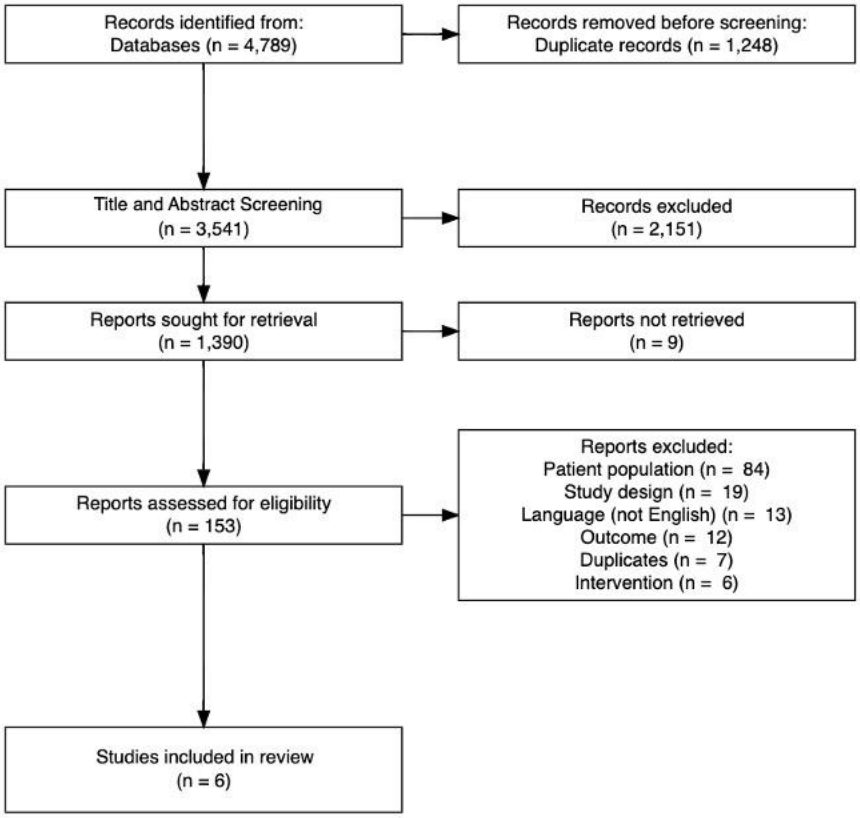

Figure 2. Network Diagrams of Pharmacological Interventions Analyzed for Each Outcome

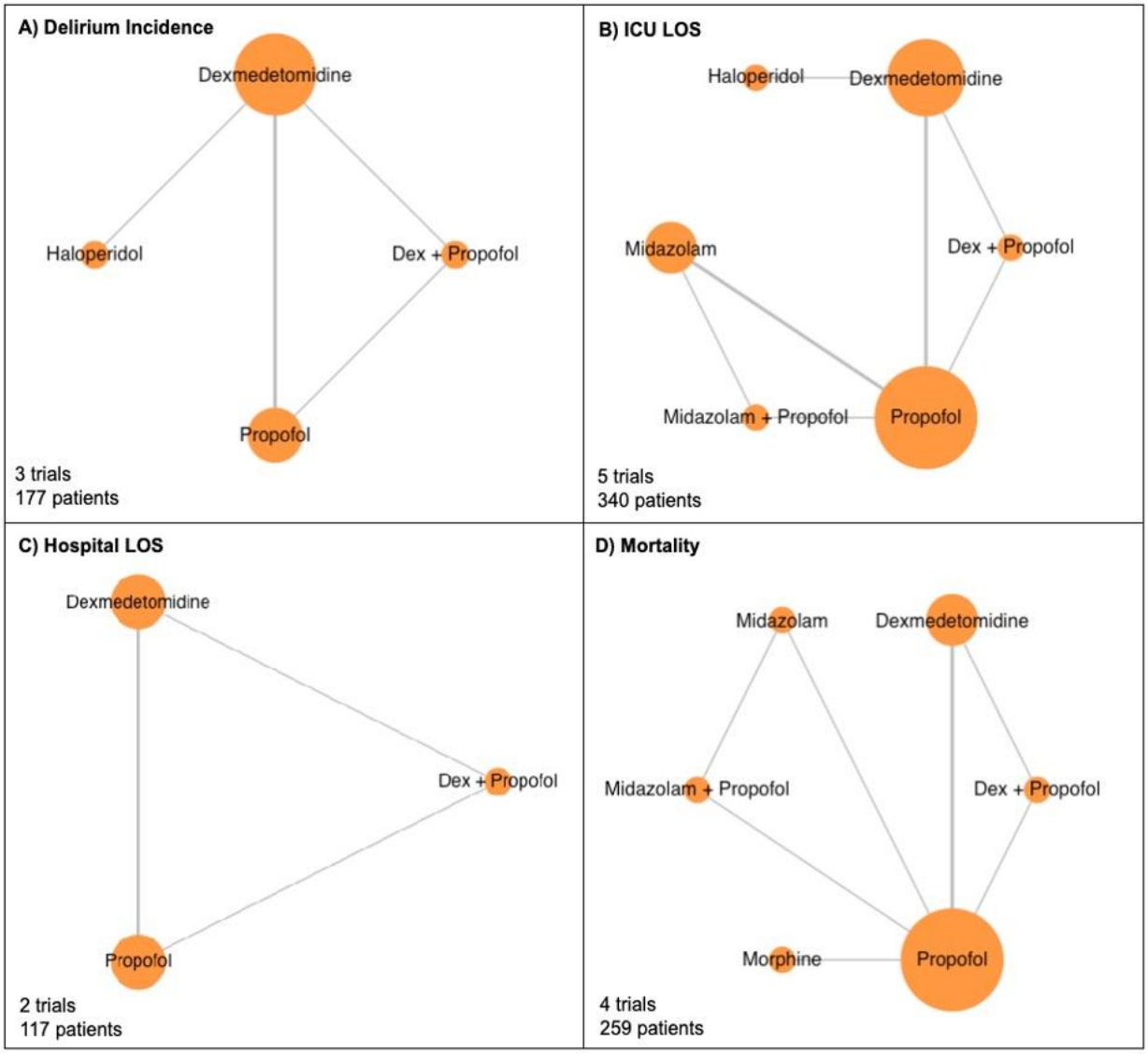

Table 1. Patient and Study Characteristics of Trials Included in Analysis

Parameter	Soltani 2021	Sanchez 1998	Kelly 1999	Camps 2000	Khallaf 2019	Winings 2021
Study Design	RCT	RCT	RCT	RCT	RCT	RCT
Sample size of each arm	Dex: 30; Haloperidol: 30	Midazolam: 34; Propofol: 33; Midazolam + propofol: 33	Propofol: 21; Morphine: 19	Midazolam: 32; Propofol: 31	Dex: 20; Propofol: 20; Dex + propofol: 20	Dex: 28; Propofol: 29
Diagnostic modality for delirium	CAM-ICU	-	-	-	CAM-ICU	CAM-ICU
Sedation goals	-	Ramsay 4-6	ICP< 20mmHg and CPP> 70mmHg	Ramsay 5-6	ICP< 20mmHg and CPP> 60mmHg	RASS 0 to -2
Country of publication	Iran	Spain	United States	Spain	Egypt	United States
Mean age, y	Dex: 40.1; Haloperidol: 36.8	Midazolam: 38; Propofol: 36; Midazolam + propofol: 32	Propofol: 39; Morphine: 33	Midazolam: 38; Propofol: 38	Propofol: 38.7; Dex: 39.3; Propofol + dex: 39.3	Dex: 53.2; Propofol: 48.2
Male, %	77	72	83	75	88	70
Head injury, %	100	59	100	73	100	0
Delirium Incidence	+	-	-	-	+	+
Length of ICU stay	+	+	-	+	+	+
Length of hospital stay	-	-	-	-	+	+
Mortality	-	+	+	-	+	+
Follow-up period for dichotomous outcomes, d	7	20	182	-	2	7
Dexmedetomidine	0.5 ug/kg every other day	-	-	-	Loading dose: 1 µg/kg Maintenance dose: 0.4–1 µg/kg/hr	0.48 µg/kg/hr
Propofol	-	1.5 mg/kg/hr	55 + - 42 µg/kg/min	1.5 mg/kg/hr	Loading dose: 1 mg/kg Maintenance dose: 1.5–4.5 mg/kg/hr	24.6 µg/kg/min
Midazolam	-	0.1 mg/kg/hr	-	0.1 mg/kg/hr	-	-
Morphine	-	-	10 +- 6.7 mg/hr	-	-	-
Haloperidol	2.5 mg over 10 mins, every 8 hours	-	-	-	-	-
Midazolam + Propofol	-	0.1 mg/kg/hr.	-	-	-	-
Propofol + Dexmedetomidine	-	-	-	-	Dex 0.2 µg/kg/hr. Propofol 2mg/kg/hr	-

Abbreviations: Dex, dexmedetomidine; ICP, intracranial pressure; CPP, cerebral perfusion pressure

Table 2. Summary of Fixed-Effects Model Measures

	Dexmedetomidine	Propofol	Haloperidol	Midazolam + propofol	Midazolam	Morphine
Comparator	**Primary outcome: Delirium (HR 95% CrI)**					
Dex + propofol	1.44 (0.39, 6.94)	2.38 (0.68, 11.36)	3.38 (0.65, 21.79)	-	-	-
Dex	-	1.66 (0.79, 3.69)	2.30 (0.88, 6.61)	-	-	-
Propofol	-	-	1.39 (0.40, 5.05)	-	-	-
	ICU LOS (Mean difference 95% CrI)					
Dex + propofol	1.19 (-0.62, 3.00)	0.61 (-1.27, 2.46)	0.80 (-2.01, 3.61)	0.20 (-6.56, 6.91)	3.03 (-1.89, 7.93)	-
Dex	-	-0.59 (-2.29, 1.11)	-0.39 (-2.54, 1.75)	0.99 (-7.68, 5.67)	1.84 (-3.02, 6.68)	-
Propofol	-	-	0.20 (-2.56, 2.90)	-0.41 (-6.86, 6.04)	2.42 (-2.12, 6.97)	-
Haloperidol	-	-	-	-0.59 (-7.63, 6.40)	2.23 (-3.09, 7.52)	-
Midazolam + propofol	-	-	-	-	2.83 (-2.69, 8.32)	-
	Hospital LOS (Mean difference 95% CrI)					
Dex+ propofol	1.59 (-0.69, 3.86)	0.15 (-2.29, 2.62)	-	-	-	-
Dex	-	-1.44 (-3.51, 0.66)	-	-	-	-
	Mortality (HR 95% CrI)					
Dex+ propofol	0.57 (0.08, 4.56)	1.16 (0.21, 7.87)	-	1.22 (0.16, 10.74)	1.37 (0.19, 11.81)	1.02 (0.11, 10.27)
Dex	-	2.02 (0.57, 8.98)	-	2.14 (0.40, 12.95)	2.42 (0.46, 14.34)	1.79 (0.27, 12.69)
Propofol	-	-	-	1.05 (0.36, 3.00)	1.18 (0.43, 3.28)	0.88 (0.22, 3.22)
Midazolam + propofol	-	-	-	-	1.12 (0.40, 3.19)	0.83 (0.15, 4.44)
Midazolam	-	-	-	-	-	0.74 (0.14, 3.80)

Abbreviations: Dex, dexmedetomidine; HR, hazard ratio; CrI, credible interval

Supplemental Materials

Table of Contents

Supplemental Materials Table 1. Search Strategy

1	exp Trauma/
2	trauma*.ti,ab.
3	(trauma* adj3 injur*).ti,ab.
4	1 or 2 or 3
5	Intensive Care Unit/
6	Respiration, Artificial/
7	(artificial respirat* or mechanical* ventilat*).tw,kf.
8	Critical Care/
9	Critical Illness/
10	(intensive care or icu or neurointensive* care or neurocritical care).tw,kf.
11	(critical* adj2 (ill* or care)).tw,kf.
12	sedati*.ti,ab.
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	4 and 13
15	randomized controlled trial.pt.
16	controlled clinical trial.pt.
17	random*.tw.
18	placebo.ab.
19	clinical trials as topic.sh.
20	trial.ti.
21	15 or 16 or 17 or 18 or 19 or 20
22	14 and 21
23	exp animals/ not humans/
24	22 not 23
25	(exp child/ or exp infant/) not exp adult/
26	((Child* or Infant* or Pediat* or Adolescen* or Neonat* or NICU) not adult*).ti.
27	24 not (25 or 26)
28	exp Delirium/
29	(delirium or confus* or delirous).tw,kf.
30	(cognit* adj2 (dysfunction or impair*)).tw,kf.
31	"Length of Stay"/
32	(length of stay or los).tw,kf.
33	Hospital Mortality/ or Mortality/
34	mortality.tw,kf.
35	((opioid* or opiate*) adj3 (dose or dosage or reduction or decreas*)).tw,kf.
36	exp Analgesics, Opioid/ad, pk [Administration & Dosage, Pharmacokinetics]
37	or/28-36
38	27 and 37
39	remove duplicates from 38

Supplemental Materials Table 2. Summary of Fixed Effects Model Fit Statistics for Each Outcome From Network Meta-Analysis

Model	Number of data points	Posterior total residual deviance	DIC*
Delirium incidence			
FE consistency	7	6.87	12.92
FE inconsistency	7	6.88	12.94
RE consistency	7	6.82	12.97
ICU LOS			
FE consistency	12	12.83	22.82
FE inconsistency	12	12.83	22.81
RE consistency	12	12.87	22.91
Hospital LOS			
FE consistency	5	4.02	8.01
FE inconsistency	5	4.02	8.00
RE consistency	5	4.00	7.97
Mortality			
FE consistency	10	8.69	16.92
FE inconsistency	10	8.67	16.9
RE consistency	10	8.07	16.61

*DIC = Deviance information criteria

Supplemental Materials Table 3. Surface Under the Cumulative Ranking (SUCRA) Scores for Each Outcome and Treatment Regimen. Values closest to 1 depict the most efficacious treatment.

	Dexmedetomidine				Midazolam		
Outcome	**+ propofol**	**Dexmedetomidine**	**Propofol**	**Haloperidol**	**+ propofol**	**Midazolam**	**Morphine**
Delirium	0.69	0.28	0.02	0.01	-	-	-
ICU LOS	0.42	0.04	0.10	0.14	0.29	0.01	-
Hospital LOS	0.54	0.02	0.44	-	-	-	-
Mortality	0.21	0.49	0.01	-	0.08	0.04	0.17

Supplemental Materials Figure 1. Risk of Bias Assessment for all Included Randomized Controlled Trials Using the Cochrane Risk-of-Bias Tool for Randomized Trials Version 2 (RoB2)

Appendix A: Submission confirmation of Chapter 3

Publication: Zitikyte, G., Roy, DC., Tran, A., Fernando, SM., Rosenberg, E., Kanji, S., Engels, PT., Wells, GA., Vaillancourt, C. Pharmacological Interventions to Prevent Delirium in Trauma Patients: A systematic review and network meta-analysis of randomized controlled trials. *Critical Care Explorations*. **Accepted January 2023**

Jan 10 2023 05:39:05:400PM

RE: CCE-D-22-00526R2, entitled "Pharmacological Interventions to Prevent Delirium in Trauma Patients: A systematic review and network meta-analysis of randomized controlled trials"

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CHAPTER FOUR: Increasing ICU Capacity by Using Dexmedetomidine as Adjunct Sedative In Trauma Patients: A health record-based mathematical model

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4.1 Preface

This chapter uses data retrieved through the electronic medical records (EPIC) database at The Ottawa Hospital, Civic Campus, to assess the current sedation practices for critically ill trauma patients and determine the impact of supplementing propofol sedation with dexmedetomidine on ICU length of stay and annual bed-capacity. Ethics approval was obtained for this study and is attached in the Appendix.

Ms. Zitikyte and Dr. Vaillancourt were responsible for conceptualization and methodology. Ms. Zitikyte was responsible for data curation, formal analysis, and writing the original draft. Dr. Vaillancourt was responsible for resources. Drs. Vaillancourt, Wells, and Tran were responsible for supervision, reviewing, and editing.

Appendix: Ethics approval from the Ottawa Health Science Network Research Ethics Board for Chapter Four

4.2 Abstract

Objective: The primary objective of this study was to determine current sedation practices and demographics in critically ill trauma patients. The secondary objective was to predict potential bed-days saved in ICU if dexmedetomidine were incorporated more into sedation practices.

Methods: We conducted a health records review (HRR) of adult trauma patients presenting to The Ottawa Hospital Level 1 trauma centre between May 1, 2020 and May 1, 2021. We included patients that were sedated with propofol and/or dexmedetomidine, and excluded those whose injuries were neither blunt nor penetrating. Ethics approval was obtained from the Ottawa Health Science Network Research Ethics Board (20220398-01H). We used the HRR results along with previous literature to inform our mathematical model assumptions to predict the impact of sedative choice on length of intensive care unit (ICU) stay.

Data Synthesis: Sixty-six (66%) of trauma ICU patients developed delirium. The majority (79%) of patients were sedated with propofol, while 18% were sedated with propofol-dexmedetomidine combination, and 3% with dexmedetomidine alone. ICU length of stay in patients with delirium was approximately twice that of patients without delirium. The mathematical model demonstrated a possible benefit between the number of patients whose propofol sedation regimen was supplemented with dexmedetomidine and the number of freed ICU bed-days per year.

Conclusions: Delirium occurs in approximately two-thirds of critically ill trauma patients and is even more prevalent in those with a traumatic brain injury. Propofol is the most used sedative but including dexmedetomidine in sedation protocols may result in shortened ICU length of stay.

4.3 Introduction

One of the most common clinical manifestations of brain dysfunction in critically ill patients is delirium.(1) It has been reported in 60-80% of mechanically intensive care unit (ICU) ventilated patients (5–7) It is defined as an acute disturbance in attention that is associated with additional cognitive impairment that is not better explained by other pre-existing or evolving neurocognitive disorders.(1,2) The diverse list of risk factors, including previous medical history, medications, severity of illness, pain management, age, surgery, alcohol use, use of physical restraints, and mechanical ventilation, make delirium difficult to predict, prevent, and treat.(4,5) Additionally, delirium has been found to be commonly unmonitored and not discussed on rounds, partially due to the sentiment that hardly anything can be done about it.(1,3) This is concerning because delirium is predictive of poor patient outcomes, including mortality, increased hospital length of stay, and increased ICU length of stay.(1,5,6)

Many hospitals have felt mounting capacity strains over the past decade, struggling in a state of operations where patient needs exceed the clinical resources available to meet them (eg. Beds, nurses, physicians, equipment).(14,15) Many hospitals across the province of Ontario have been filled beyond 100% capacity since 2019, leaving no reserve for any sudden influx, like the COVID-19 pandemic.(16) In Ontario, the number of acute care beds has remained relatively stable at 20,000 over the past 20 years despite an increase in population of over three million people.(17,18) The increased strain has challenged both system resources and provider cognitive bandwidth, negatively impactive patient care.(14,15)

An important area for delirium and length-of-stay mitigation is choice in sedation. Studies consistently report a reduction in delirium incidence with propofol or dexmedetomidine when compared to benzodiazepines, haloperidol, or risperidone.(1,8–11) The Clinical Practice

Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) suggest using non-benzodiazepines (propofol or dexmedetomidine) for sedation in critically ill, mechanically ventilated patients due to reductions in ICU stay and delirium.(12) The benefits are not limited to patient outcomes, but expand to hospitals as well. With tens of millions of additional inpatient days and billions of dollars associated with delirium annually, decreased delirium is associated with decreased length of ICU and hospital stay and increased cost-savings.(13)

The overall objective is to decrease delirium among critically ill trauma patients. Specifically, we intend to 1) Study patient and system characteristics that lead to delirium through a health records review, and subsequently 2) Apply literature-based assumptions in a mathematical model to estimate the potential benefit of using dexmedetomidine in the ICU trauma population.

4.4 Methods

4.4.1 Health Records Review

Study Design and Setting

We conducted a health record review of trauma patients aged 16 years or older presenting between May 1, 2020 and May 1, 2021 to The Ottawa Hospital Level 1 trauma centre. The Ottawa Hospital is the only Level 1 trauma centre for the Ottawa region with a population of approximately one million.(18) Per year, it treats over 700 major (injury severity score >= 12 or code 1) traumas and admits approximately 100 of those patients to the ICU.(19) We were guided by Gearing et al's published article on methodology for conducting retrospective chart reviews.(20)

Study Population

Patients were eligible if they were admitted to the ICU with a traumatic injury and required sedation. Patients were included if they were sedated with propofol, dexmedetomidine, or a combination of the two. Patients were excluded if their injury was neither blunt nor penetrating (e.g. drowning, burning, shock). There were no limitations based on injury severity score or presence of traumatic brain injury.

Ethics

The Ottawa Hospital's research ethics board reviewed and accepted the study protocol. Informed consent was not required due to the retrospective nature of the study; patients all received standard of care and were not randomized. Patient confidentiality was maintained throughout the study.

Case Identification and Data Collection

Participants were identified using a list provided from the local trauma database. Data was manually collected from Epic (Epic Systems Corporation, Madison, Wisconsin, USA) and entered into a password-protected, piloted data collection form. We collected demographics (age and sex), injury type (e.g. blunt or penetrating), traumatic head injury (yes/no), length of ICU stay (days), length of hospital stay (days), mortality (yes/no), mechanical ventilation (yes/no), primary sedative used, and delirium occurrence (yes/no). Delirium was defined as a positive CAM-ICU score.

Data Analysis for Health Record Review

We report patient and system characteristics over a one-year period using simple descriptive statistics using Rstudio version 4.2.1.(21)

4.4.2 Mathematical Model

We developed a mathematical model to predict the impact of various sedatives on length of ICU stay and total freed bed-days per year.

Study Population

Participants included in the health records review were included in the mathematical model, with one exception: We excluded patients who were treated with dexmedetomidine-alone. The decision to exclude dexmedetomidine-only patients was based on several factors. First, at this early stage in research it is more realistic for decision makers to supplement their propofol-sedated trauma patients with dexmedetomidine, rather than switch out propofol for dexmedetomidine entirely. Second, although a protocol with propofol-dexmedetomidine appears superior on rates of delirium compared to dexmedetomidine-alone, the addition of propofol to dexmedetomidine-only would necessitate mechanical ventilation due to respiratory depression.(22) Neither of the two patients from the health records review who were treated with dexmedetomidine-only were mechanically ventilated, which itself is a risk factor for delirium and predictor of increased length of ICU stay.(23) The heterogeneity between the two non-mechanically ventilated patients and the remainder of the cohort was such that it was not appropriate to apply the math model assumptions to these two patients.

Assumptions

The assumptions for the mathematical model were based on baseline characteristics from this health record review alongside reported literature.

1 – Delirium incidence in critically ill trauma patients is 60% at baseline

Lat et al. studied 134 consecutive patients admitted at two tertiary, level 1 trauma center

ICUs requiring mechanical ventilation. Delirium was assessed daily using the validated CAM-ICU tool. 63% of patients developed delirium during their stay in the ICU.(3) Our health records review also found that 66% of ICU trauma patients developed delirium throughout their stay. For the purposes of our mathematical model, we assume a delirium incidence of 60%.

2 – Delirium incidence in trauma ICU patients is 0.42 times lower when treated with a combined propofol-dexmedetomidine sedation regimen

We recently completed a systematic review and network meta-analysis that compared the effectiveness of pharmacologic interventions in preventing delirium in critically ill trauma patients. Four treatment regimens were compared through three trials and the authors found that when compared to propofol-alone, the odds of developing delirium when sedated with a propofol-dexmedetomidine combination was 0.42 (95% CrI 0.09-1.47). While the NMA was unable to conclude that a difference between sedatives exists, the probability distributions favouring dexmedetomidine are consistent with other studies where delirium incidence was lower with dexmedetomidine than with propofol.(12) We include 95% credible interval estimates in all math model calculations to emphasize caution in interpreting the results.

3 – ICU length of stay is 50% shorter in patients who do not develop delirium compared to those who do.

In their study assessing the impact of delirium on ICU LOS in surgical and trauma patients, Lat et al. saw a 50% decrease in ICU LOS for patients who did not develop delirium.(3) This is consistent with the results of our health records review, where non-delirious trauma patients spent approximately half the time in the ICU as their delirious counterparts. For the sake of this exercise, we are assuming the relationship is causal.

4 – ICU length of stay for all patients who develop delirium is 8 days

Our health records review found that patients who developed delirium spent a median of 6 days (IQR 11) in the ICU. A prospective study of 134 critically ill trauma patients by Lat et al found that delirious patients spent an average of 12 days in the ICU, and a case-control study of 265 trauma patients by Blondell et al found an average ICU length of stay of 8.7 days in trauma patients.(24) We averaged these values to inform our assumption that all delirious trauma patients spend an average of 8 days in the ICU. We did not find a large difference between median length of ICU stay in propofol versus propofol-dexmedetomidine patients (7.5 days with IQR 12.75, and 6 days with IQR 3.25, respectively). This is in line with several studies who compared propofol against propofol-dexmedetomidine on ICU length of stay in critically patients.(25,26) Therefore, we applied this assumption irrespective of type of sedation protocol.

Modelling

We began our model by determining the current baseline rates for sedation with propofol and propofol-dexmedetomidine at the level 1 trauma centre in Ottawa, Canada, from the health records review. In line with the first assumption, 60% of patients sedated with propofol were assumed to develop delirium during their stay. In line with the second assumption, delirium incidence in the propofol-dexmedetomidine group was assumed to be 42% that of the propofol group. In line with the fourth assumption, all delirious patients were assumed to spend approximately eight days in the ICU; non-delirious patients were assumed to spend half of that time (4 days) in the ICU.

We then adjusted sedation rates such that there was a five percent increase in the proportion of patients who received propofol-dexmedetomidine while a simultaneous five percent decrease in the proportion of propofol-only patients occurred. This allowed us to observe the potential number of days that could be freed in the ICU, per year, if more patients were

sedated with a propofol protocol that included adjunctive dexmedetomidine. We performed this exercise until we reached an 80% sedation rate with propofol-dexmedetomidine.

Additionally, we used the 95% CrI from the network meta-analysis point estimate, when calculating delirium incidence in propofol-dexmedetomidine patients, to create upper and lower bounds for our mathematical model results.

4.5 Results

4.5.1 Retrospective Health Records Review

We screened 213 trauma codes, of which 68 were adult trauma patients who were admitted to the ICU between May 1, 2020 and May 1, 2021 with blunt or penetrating injury and required sedation. One (1.5%) was excluded because their sedation regimen did not include propofol nor dexmedetomidine, leaving 67 cases for study inclusion (Figure 1).

Patient characteristics for all 67 patients are summarized in Table 1. Patients were predominantly male (75%), with an average age at time of injury of 47 [range 17-96] years old. Fifty-eight (87%) patients presented with blunt injuries and 9 (13%) with penetrating injuries; 29 (43%) of patients had a TBI; and 14 (21%) of patients died during their hospital stay. Mechanical ventilation was required in 65 (97%) patients. Propofol was the primary sedative used for 53 (79%) patients, 12 (18%) were sedated with propofol and dexmedetomidine combined, and 2 (3%) were sedated with dexmedetomidine. Of those with a TBI, 72% developed delirium. Delirium, as defined by a positive CAM-ICU score, occurred in 44 (66%) of patients. Average age, mechanical ventilation, type of injury, primary sedative, and mortality rates were approximately consistent between the two groups.

Because of the small number of patients, we compared both mean and median length of stays to determine any skewed effects. The difference between the two was clinically important,

with the mean skewing towards longer lengths of stay, so we opted to present point estimates as a median with interquartile ranges (IQR) to remain robust against outliers. The median ICU length of stay for delirious and non-delirious patients were 6 and 3 days, respectively. The total number of occupied ICU bed-days for this cohort was 554 days.

This study was not designed to perform statistical comparisons between delirious and non-delirious cohorts. With a small event rate of only 40 cases of delirium, performing multiple comparisons between groups could render us vulnerable to spurious findings.(26) Thus, we focused on visual inspection instead. Trauma patients who screened positive for delirium during their ICU admission seemed to spend approximately twice as much time in both the ICU and hospital compared to non-delirious patients. The proportion of males in the delirious group was higher than females. The proportion of blunt versus penetrating injury was relatively similar between groups.

4.5.2 Mathematical Model

We included 65 (96%) patients from the chart review. Two (3%) patients who were not mechanically ventilated were excluded.

Using the mathematical model, we predicted the overall ICU bed-days incurred and the number of freed bed-days per year according to variable sedative regimes as illustrated in Figures 2 and 3. Currently, approximately 20% of ICU trauma patients are sedated with a combined propofol-dexmedetomidine regime (Table 1). “Freed bed-days” calculation was based on the difference between the calculated number of bed-days that would be occupied per year with 20% propofol-dexmedetomidine sedation, matching the proportions observed in the health records review. For every 3 additional trauma ICU patients (5%) who’s sedation regimen of

propofol is adjusted to include dexmedetomidine, the number of available bed-days per year could increase by approximately 5 days (Table 3).

4.6 Discussion

This health records review and mathematical model describes current sedation practices at The Ottawa Hospital, Civic Campus, and identifies the potential impact on hospital resources and capacity with adjunctive dexmedetomidine sedation. In the review, we found that 66% of our trauma ICU patients develop delirium with the majority (79%) receiving propofol sedation. Eighteen percent are sedated with propofol-dexmedetomidine combination and three percent with dexmedetomidine alone. Patients who develop delirium tend to remain in the ICU for twice as long as non-delirious patients. The mathematical model demonstrated a positive relationship between the number of patients whose propofol sedation regimen is supplemented with dexmedetomidine and the number of annually freed ICU bed-days. Approximately five ICU bed-days could be freed, per year, for every three additional patients who receive adjunctive dexmedetomidine with propofol.

Previous Studies

Currently, no clear evidence exists for sedative choice to prevent delirium in critically ill trauma patients. Guidelines are based on general ICU patients and other indicators (e.g. agitation, mechanical ventilation requirements).(12) Existing trauma sub-studies are heterogenous; some find clear benefit with dexmedetomidine while others find no significant difference when compared to propofol.(25,28,29)

Based on other populations, there appears to be potential benefit with dexmedetomidine. A 2013 systematic review and meta-analysis by Xia et al looked at ten randomized controlled trials that compared dexmedetomidine and propofol for sedation in adult, mechanically

ventilated ICU patients.(30) Xia et al found that dexmedetomidine significantly reduced delirium incidence. However, no subgroup analysis for trauma patients was reported.

A 2019 systematic review and network meta-analysis by Burry et al found that dexmedetomidine may reduce delirium duration when compared to placebo, but this was also amongst all ICU patients.(31) Additional evidence for dexmedetomidine's benefit exists among the cardiac population. Djaiani et al conducted a randomized controlled trial in older patients undergoing cardiac surgery and found that dexmedetomidine significantly reduced delirium incidence when compared to propofol patients.(32) Though the heterogeneity between cardiac and trauma patients does not facilitate the generalizability of these results.

Clinical Implications

Delirium is a complex disorder that is exceptionally common in critically ill trauma patients.(33) Not only does cost the healthcare system billions annually, but also leads to poorer patient outcomes and increased strain.(3,13,33) With an increasing population and viral pandemics and epidemics, ICUs especially are feeling the burden of illness severity.(14,15) Healthcare organizations are struggling and baseline ICU capacity must be expanded significantly with additional surge capacity built in.(34) Increasing the use of dexmedetomidine as an adjunct to propofol sedation could be a potential area for mitigating ICU length of stay and freeing capacity for additional critically ill patients. This could, in turn, improve patient outcomes and decrease ICU costs associated with their stay.

Research Implications

Echoing the PADIS guidelines, the evidence for dexmedetomidine is relatively sparse with low certainty and larger, and well-conducted studies are required to assess its benefit in critically ill trauma patients and comparison with propofol.(12) Larger studies with more patients

and covariates are required to improve evidence quality and precision for the critically ill trauma subpopulation. Propensity score-matching or regression modelling would decrease the reliance on assumptions and allow for a stronger understanding of risk factors related to delirium and ICU length of stay. Additionally, a formal cost-analysis would be helpful to understand the difference in resource utilization between dexmedetomidine and propofol groups.

Strengths and Limitations

Strengths of this study include its focus on the use of dexmedetomidine in a minimally studied cohort of critically ill trauma patients. The retrospective design provided a basic, informative overview of current practices and outcomes of trauma patients at Ottawa's Level 1 trauma centre. Additionally, the use of Epic software at The Ottawa Hospital facilitated accurate, up-to-date, and complete information about patients during their hospital stay.

There are several limitations to this study. First, the health records review is not a randomized controlled trial, thus selection bias could exist between trauma patients who received adjunctive dexmedetomidine versus those who did not. Second, delirium can be under-documented and under-recognized, especially the hypoactive subtype as is common in sedated patients.(4) We defined delirium as patients who had a positive CAM-ICU order in their EPIC chart, but the number of delirious patients could be higher than what was extracted from the health records review. Third, the CAM-ICU does not account for severity of delirium, so we are unable to comment on the severity of illness between both groups. Additionally, we did not have parameters around what constituted a combined propofol-dexmedetomidine sedation regimen other than both sedatives had to have been administered during the ICU stay. This means this study is unable to distinguish between differences in sequence or dose-duration. Some patients

may have received mostly propofol with some dexmedetomidine, or mainly dexmedetomidine with some propofol. Lastly, the small number of patients decreases the power of estimates.

4.7 Conclusion

Delirium is a key predictor of increased hospital burden and poorer patient prognosis. Despite implementation of validated screening tools and an overall culture of decreased over-sedation, delirium continues to burden the healthcare system. This study examines current sedation practices at a Level 1 trauma centre and demonstrates the potential benefit of sedation choice on ICU bed-availability.

4.8 References

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4.9 Figures and Tables

Table 1. Patient Characteristics of Delirious and Non-Delirious Critically Ill Trauma Patients over the 1-year Period

Characteristics	**N = 67**	**Delirious (N=44)**	**Non-delirious (N=23)**
Age, mean (SD)	47.0 (20.5)	46.2 (19)	48.0 (24)
Male, No. (%)	50 (75)	37 (84%)	14 (58%)
Head Injury, No. (%)	29 (43)	21 (48%)	8 (35%)
Injury Type			
Blunt	58 (87)	37 (84%)	21 (92%)
Penetrating	9 (13)	7 (16%)	2 (8%)
Mechanical Ventilation, No. (%)	65 (97)	42 (95%)	23 (100%)
Delirium, No. (%)	44 (66)	-	-
Primary Sedative No. (%)			
Propofol	53 (79)	34 (77%)	19 (83%)
Propofol +	12 (18)	1 (18%)	1 (17%)
Dexmedetomidine	2 (3)	2 (5%)	0 (0%)
Dexmedetomidine			
Hospital LOS, median (IQR)	24.0 (21.7)	28.5 (23)	16.4 (17)
ICU LOS, median (IQR)	5 (9)	6 (11)	3 (7)
Total ICU Bed-days	554		
Mortality, No. (%)	14 (21)		

Abbreviations: SD (Standard Deviation); IQR (Interquartile Range); ICU (Intensive Care Unit); LOS (Length of Stay)

Table 2. Median Length of Stay for Sedated and Mechanically Ventilated Trauma Patients in the Intensive Care Unit Based on Sedative Used and Delirium Incidence

Trauma	Sedative used (n=65, %)	Delirium (n=65, %)	ICU LOS Median (IQR)	Total ICU bed-days incurred
N = 65	Propofol (n=53, 79%)	Yes (n=34, 64%)	7.5 (12.75)	554
		No (n=19, 36%)	3 (8)	
	Propofol + Dexmedetomidine (n=12, 18%)	Yes (n=8, 67%)	6 (3.25)	
		No (n=4, 33%)	3 (2.75)	

Abbreviations: IQR (Interquartile Range); ICU (Intensive Care Unit); LOS (Length of Stay)

Table 3. Predicted Occupied ICU Bed-Days and Number of Freed ICU Bed-Days by sedated and mechanically ventilated trauma patients per Year, According to Variable Rates of Sedation with Propofol-Dexmedetomidine Combination at the Civic Campus of The Ottawa Hospital

Variable propofol-dexmedetomidine sedation rates (%)	Total bed-days per year N (95% CrI)	Freed bed-days per year † N (95% CrI)
20*	398 (386-408)	0 (-10-12)
25	393 (379-406)	5 (-8-19)
30	389 (371-404)	9 (-6-27)
35	384 (363-402)	14 (-4-34)
40	380 (356-399)	19 (-1-42)
45	375 (349-397)	23 (1-49)
50	371 (342-395)	27 (3-56)
55	366 (334-393)	32 (5-64)
60	362 (327-391)	36 (7-71)
65	357 (319-389)	41 (9-79)
70	353 (312-387)	45 (11-86)

Abbreviations: ICU (Intensive Care Unit); CrI (Credible Interval)
* Current rate of propofol-dexmedetomidine sedation in trauma ICU patients
† Determined by subtracting the total bed-days per year from the baseline estimate of bed-days per year (398)

Figure 1. Profile of Critically Ill Trauma Patients Included in the Retrospective Chart Review and Mathematical Model

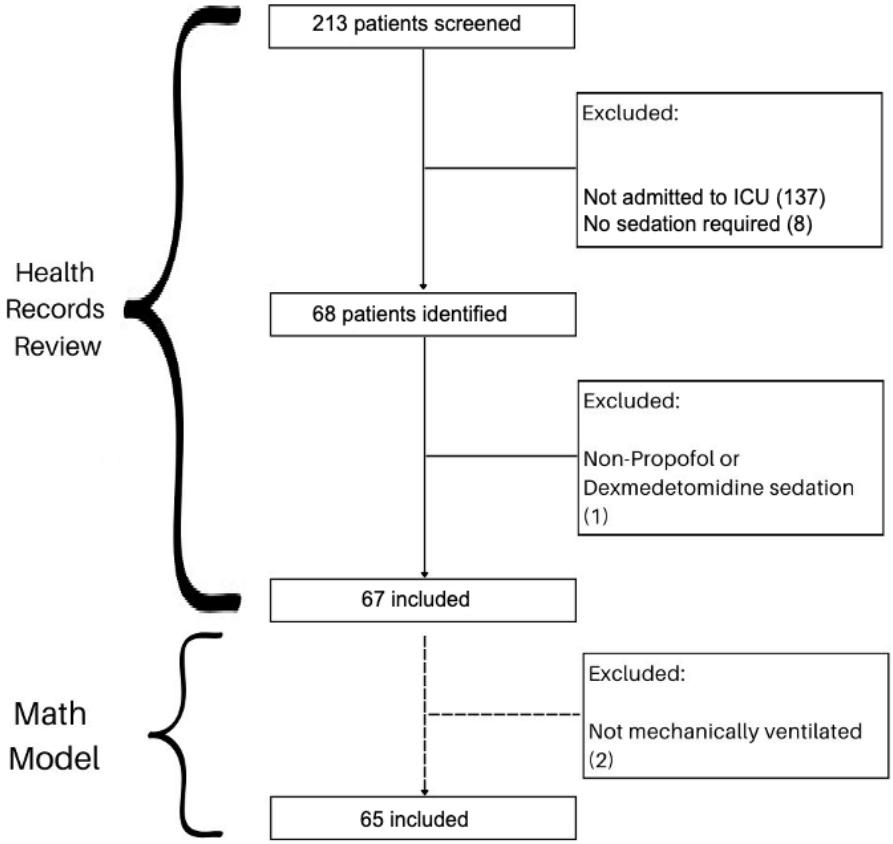


Figure 2: Mathematical Model for Predicting Length of Stay in the Intensive Care Unit and Additional Freed Bed Days per Year According to Predetermined Rates of Sedation Use

		%	N (delirium)	ICU LOS	N (Bed-days)
Sedative A	Delirium	C	A*C	8	[1]
	No Delirium	1 – C	A*(1-C)	4	[1]
Sedative B	Delirium	C*0.42	B*C*0.42	8	[1]
	No Delirium	1 – (D*0.42)	B*[1-(C*0.42)]	4	[1]
Total = A+B				Tot. Bed-days per year (N)	[2]
				Freed bed-days per year (N)	[3]

A = N propofol
B = N propofol + dexmedetomidine
C = Assumed delirium rate in propofol cases
D = Average ICU LOS in delirious patients (8 days)
E = Baseline total ICU days at The Ottawa Hospital for trauma patients

Where:
[1] = N (delirium) * ICU LOS
[2] = ∑ [1]
[3] = E – [2]

Where:
- Delirium in the propofol + dexmedetomidine group is 0.42 times that of the propofol group
- ICU LOS is half as long in patients who do not develop delirium

Abbreviations: ICU (Intensive Care Unit); LOS (Length of Stay)

Figure 3. Predicted Count of Total Occupied ICU Bed-Days in the Intensive Care Unit by Sedated and Mechanically Ventilated Trauma Patients According to Variable Rates of Sedation with Propofol-Dexmedetomidine

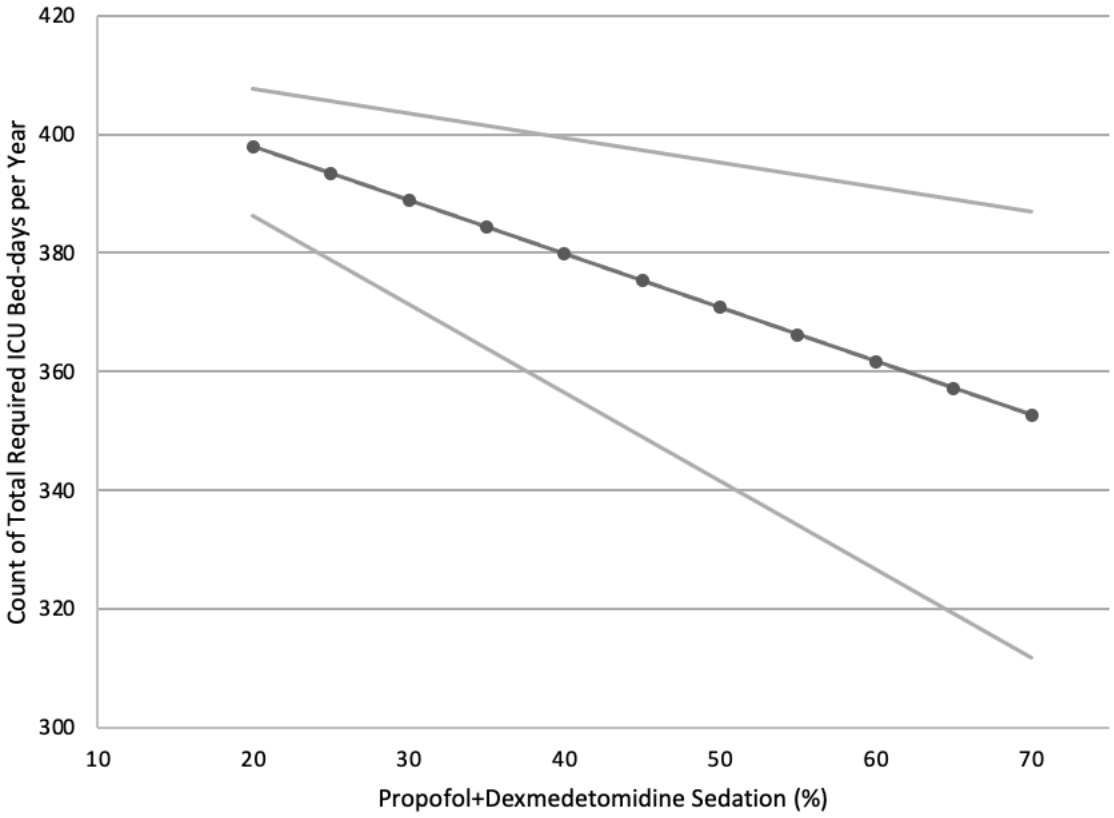
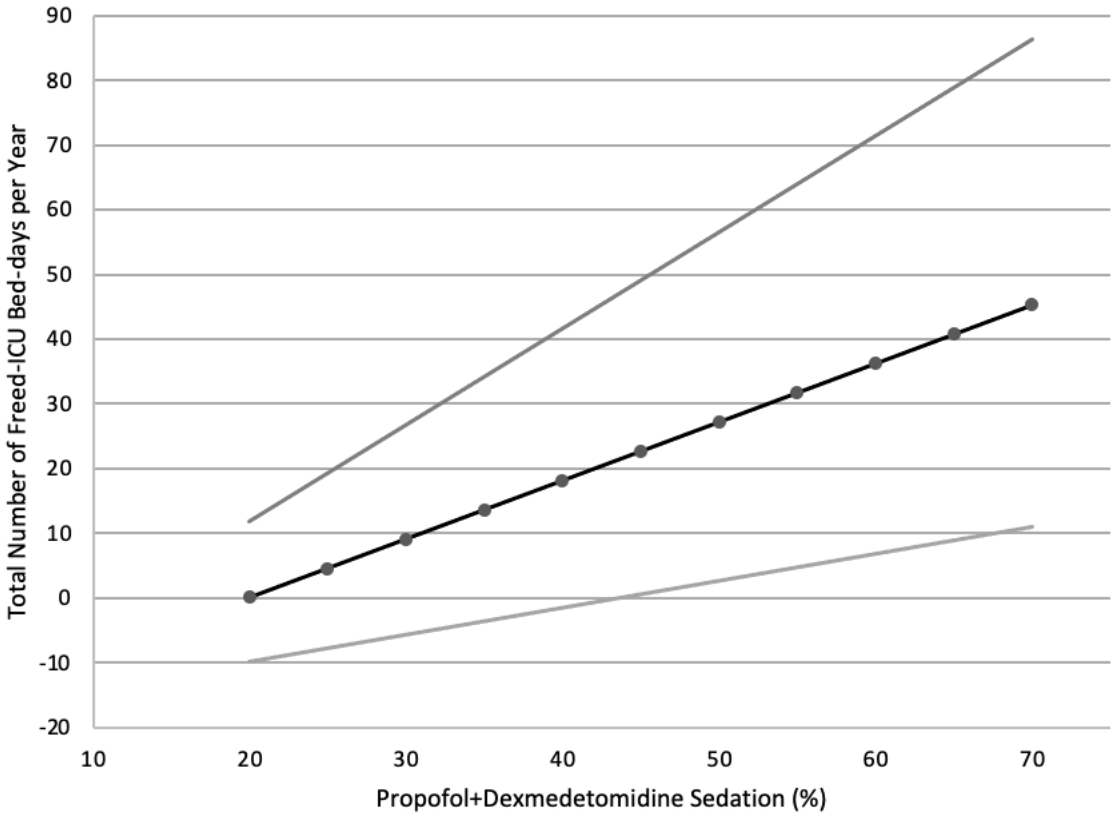


Figure 4. Predicted Intensive Care Freed Bed-Days per Year According to Variable Rates of Sedation with Propofol-Dexmedetomidine Combination at the Civic Campus of The Ottawa Hospital



Appendix B: Ethics approval from the Ottawa Health Science Network Research Ethics Board for Chapter Four

July 04, 2022

Dr. Christian Vaillancourt

Ottawa Hospital - Civic Campus
Department of Emergency Medicine
1053 Carling Avenue, F658
Ottawa, ON K1Y 4E9

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

Protocol ID#: 20220398-01H;

Reducing delirium and enhancing cost-effectiveness with dexmedetomidine in trauma patients: a health record-based mathematical model

Dear Dr. Christian Vaillancourt,

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 REBadministration@ohri.ca or 613-798-5555 extension 16719.

CHAPTER FIVE: CONCLUSION

This manuscript-based thesis has aimed to answer two questions: 1) Is there a difference in effectiveness between pharmacological interventions on delirium incidence in trauma ICU patients; and 2) Could the use of dexmedetomidine improve patient outcomes and hospital resource-use?

5.1 Overview

In Chapter 2, we described the epidemiology and challenges of predicting delirium in critically ill trauma patients. We reviewed the current literature for current recommendations, guidelines, and expanded on the heterogeneity between critically ill patients and critically ill *trauma* patients. We discussed that the choice of sedatives is a promising area for delirium mitigation, with a focus on alpha-2 agonist, dexmedetomidine. In Chapter 3, we conducted a systematic review and network meta-analysis to assess the effectiveness of available pharmacological interventions on delirium incidence in the trauma ICU population. We also included related secondary outcomes such as ICU length of stay, hospital length of stay, and in-hospital mortality. In Chapter 4, we performed a health records review and created a mathematical model. With the health records review, we examined trauma ICU patient demographics and current sedation practices with dexmedetomidine and propofol at the Civic Campus of The Ottawa Hospital. Based off the results of the systematic review and network meta-analysis and the health records review, we formulated assumptions and created a mathematical model to understand the real-world implications of integrating dexmedetomidine into sedation practices. The primary outcome of interest was the total required ICU bed-days for the cohort, along with how many potential bed-days could be freed in the ICU annually.

5.2 Key Findings

We generated two manuscripts from this thesis. The first examined the effectiveness of dexmedetomidine compared to other pharmacological interventions in critically ill trauma patients, while the second helped understand current sedation practices and informed potential impact on hospital resources. The first manuscript reported a systematic review and network meta-analysis with the following findings: 1) no difference was found between any of the studied pharmacological interventions on delirium incidence, ICU length of stay, hospital length of stay, and mortality; 2) estimated probabilities indicate a potential benefit exists with dexmedetomidine-alone and propofol-dexmedetomidine-combined; and 3) larger, well-conducted studies are essential to narrow the precision of evidence on this topic.

The second manuscript reported on a health records review and mathematical model that described current sedation practices at The Ottawa Hospital, Civic Campus, and identified potential impact on hospital resources and capacity with adjunctive dexmedetomidine sedation. We found that 66% of our trauma ICU patients develop delirium. The majority (79%) of patients are sedated with propofol, while 18% are sedated with propofol-dexmedetomidine combination, and 3% with dexmedetomidine alone. We also found that the ICU length of stay in patients with delirium is approximately double that of patients without delirium. The mathematical model demonstrated a positive linear trend between the number of patients whose propofol sedation regimen is supplemented with dexmedetomidine and the number of freed ICU bed-days.

5.3 Previous Studies

Most research that focuses on delirium and preventative tactics in the ICU assess patients as a generalized population. Previous systematic reviews have found potential benefit in delirium occurrence and related patient outcomes with dexmedetomidine, but these results are largely based on moderate to low evidence and is limited in its generalizability to trauma patients.(1,2)

In Chapter 2, we discussed that trauma patients tend to be younger than general ICU patients, are more likely to have a traumatic brain injury, and are most often dealing with a much higher burden of acute pain.(3) These patients are more likely to present with positive toxicology screens for alcohol and/or drugs; and are most often fully sedated and intubated.(3) Yet, many of the above are not taken into consideration when applying the same prediction models, guidelines, and diagnostic methods that are designed for the entire ICU population.(1,4) Our network meta-analysis was unique in that it was the first to compare sedative agents with a focus solely on the critically ill trauma population. While the results cannot guide practice changing inferences, they are promising in that they do not indicate clear inferiority of dexmedetomidine compared to other sedatives.

With regards to current recommendations for dexmedetomidine use in critically ill trauma patients, the PADIS guidelines found no important differences in outcomes between dexmedetomidine and propofol and noted that incorporating both sedatives into practice for critically ill patients was likely acceptable and feasible.(1) Our health records review found that approximately 20% of patients are already receiving dexmedetomidine, either alone or as an adjunct to propofol. Based on PADIS guidelines, it is reasonable to utilize dexmedetomidine more often, at minimum as an adjunct to propofol. Additionally, several studies have evaluated and concluded that dexmedetomidine's safety is comparable to propofol's among traumatic brain injury patients, of which there were over 40% in our review.(5–8) The similar ICU length of stays between delirious and non-delirious patients in each sedative group indicates that there are many factors adding complexity to both delirium and associated outcome prognosis. Our mathematical model showed a consistent positive, linear trend favouring adjunctive

dexmedetomidine-propofol sedation, compared to propofol-alone, for potentially increasing hospital capacity via freed bed-days.

5.4 Research Implications and Next Steps

A consistent theme across the articles in this thesis is the limitation in number of studies and patients available for comparison. The analysis and assessment of dexmedetomidine in the critically ill trauma population is still relatively young and in the process of building the foundation for larger, well-conducted trials to stand upon. In saying that, it would be reasonable to start taking those steps forward: to build off both these manuscripts and the remaining cohort of trauma delirium research to perform a large, prospective multicenter observational study focusing solely on critically ill trauma patients, or a pilot study where all confounders can be controlled for and/or mitigated.

5.5 Strength and Limitations

This thesis has several strengths. The systematic review and network meta-analysis was conducted thoroughly with a rigorous search strategy. We adhered to the well-established PRISMA guidelines for network meta-analysis when reporting our outcomes. To our knowledge, this was the first network meta-analysis comparing pharmacological interventions for delirium prevention in the critically ill trauma population. By performing a network meta-analysis, we were able to simultaneously compare several interventions using direct and indirect evidence. Our search strategy included a broad scope of comparators and outcomes to ensure inclusion of as many studies that connected to our network. We only included randomized controlled trials to ensure the highest level of evidence, and the studies had low risk of bias across all domains. The limitations of the systematic review include the low number of available studies to compare; there were a couple that could not be included because they did not have a connecting node with

the network. Additionally, none of the articles excluded for language were eligible and would not have changed the findings. The sparsity of the network prevented us from being able to perform GRADE assessments, and the wide credible intervals indicate imprecision between the results of the studies that were included.

Our health records review and mathematical model had several strengths. The chart review form was carefully designed a priori and methodological guidelines were followed. The assumptions for the mathematical model were all based on previous literature and results obtained from our reviews. Limitations of this study include its retrospective nature. Our results relied on what was documented by the health care teams; we had planned to collect information on injury severity but over half the patients did not have a score documented. Additionally, the definition for combined propofol and dexmedetomidine sedation was if the patient was documented to have received both during their ICU stay. Some patients received both concomitantly, while others received one for a few days and the other for a few days, and both are categorized under the same heading. Lastly, the small number of reviewed patients decreases power and precision of results.

5.6 Conclusion

Delirium is associated with negative patient outcomes and increased healthcare costs. While no difference was found between any pharmacological interventions on delirium incidence, estimated probabilities from the systematic review and network meta-analysis suggest that there could be some benefit from adjunctive dexmedetomidine with propofol in trauma ICU patients. The results of the math model further emphasize the potential gain in resources that hospitals could see if more trauma patients were sedated with a combined propofol-dexmedetomidine regimen. This thesis lays the groundwork that supports the urge for larger,

well-conducted research and randomized-controlled trials on sedation with dexmedetomidine in ICU trauma patients.

5.7 References

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