EFFICACY AND SAFETY OF INTRANASAL KETAMINE FOR ACUTE PAIN MANAGEMENT IN THE EMERGENCY SETTING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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DISSERTATION SUBMITTED IN PARTIAL FULLFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE

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AKU JANJI

Diperakui bahawa disertasi yang bertajuk EFFICACY AND SAFETY OF INTRANASAL KETAMINE FOR ACUTE PAIN MANAGEMENT IN THE EMERGENCY SETTING: A SYSTEMATIC REVIEW AND META-ANALYSIS merupakan kerja and penyelidikan yang asli dari SEAK YEE SIN, No. Kad Pengenalan 880310-35-5092, No. Matrik P-UM0372/18 dari tempoh 2018 hingga 2022 aadalah di bawah penyeliaan kami. Disertasi ini merupakan sebahagian daripada syarat untuk penganugerahan Sarjana Perubatan Kecemasan, segala hasil penyelidikan dan data yang diperolehi adalah hak milik terpelihara Universiti Sains Malaysia.

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Tandatangan Pelajar

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Tandatangan Penyelia

Pensyarah Jabatan Perubatan Kecemasan

Pusat Pengajian Sains Perubatan

Universiti Sains Malaysia

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Tandatangan Ketua Jabatan

Jabatan Perubatan Kecemasan

Pusat Pengajian Sains Perubatan

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I would also like to extend my deep and sincere gratitude to my co-supervisor, Dr. Md Asiful Islam for his valuable and constructive ideas during the planning and development of this dissertation. All the teachings and knowledge shared with me are very much appreciated. This dissertation would not be completed without his support and encouragement.

In addition, I wish to thank various people for their contributions to this dissertation including my co-authors, Head of Department, all the emergency physicians in the Department of Emergency Medicine, Hospital Universiti Sains Malaysia, librarians of Hamdan Tahir Library, Universiti Sains Malaysia as well as my fellow colleagues. Their precious assistance and tremendous feedbacks had inspired me to complete this project in a timely manner.

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LIST OF ABBREVIATIONS

IV	Intravenous
ED	Emergency department
IN	Intranasal
CI	Confidence interval
MD	Mean difference
OR	Odds ratio
PROSPERO	International Prospective Register of Systematic Reviews
ACEP	American College of Emergency Physicians
RSI	Rapid sequence intubation
NMDA	N-methyl-D-aspartate
CNS	Central nervous system
IM	Intramuscular
RCT	Randomised controlled trial
NRS	Numeric rating scale
VAS	Visual analogue scale
SRMA	Systematic review and meta-analysis
WHO	World Health Organization's

JBI	Joanna Briggs Institute
RevMan	Review Manager
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
LDK	Low-dose-ketamine

ABSTRACK

Pengenalan

Pengurusan kesakitan akut selalunya tidak optimum di Jabatan Kecemasan disebabkan kesesakan, kekurangan kakitangan, atau kanulasi intravena (IV) yang bermasalah. Objektif kajian sistematik dan meta-analisis ini adalah untuk menilai keberkesanan dan keselamatan ketamin intranasal (IN) untuk sakit akut bagi orang dewasa dalam keadaan kecemasan.

Kaedah

Kami telah mencari dan mengenal pasti kajian melalui PubMed, Scopus, Web of Science, Cochrane Database dan Google Scholar sehingga 21 Mei 2021. Model kesan rawak dengan 95% selang keyakinan (CI) digunakan untuk menganggar perbezaan min (MD) dan nisbah ganjil (OR). Statistik I^2 dan ujian Q Cochran digunakan untuk menentukan heterogeniti.

Keputusan

Tujuh ujian rawak terkawal telah dimasukan dengan 1760 pesakit. Tiada perbezaan ketara dalam skor kesakitan yang membandingkan ketamin IN dengan analgesik IV atau plasebo pada 5 (MD 0.94, p = 0.26), 15 (MD 0.15, p = 0.74), 25 (MD 0.24, p = 0.62), 30 (MD -0.05, p = 0.87), dan 60 (MD -0.42, p = 0.53) minit. Ia juga tiada perbezaan yang signifikan dalam keperluan analgesik penyelamat antara ketamin IN dan analgesik IV (OR 1.66, 95% CI: 0.57-4.86, p = 0.35, I2 = 70%). Hanya kesan sampingan yang ringan terlihat pada pesakit yang menerima ketamin IN.

Kesimpulan

Keputusan kami menunjukkan tiada perbezaan antara ketamin IN dan analgesik IV. Ketamin IN mungkin mempunyai peranan dalam pengurusan kesakitan akut di kalangan orang dewasa di Jabatan Kecemasan.

Nombor pendaftaran percubaan: PROSPERO CRD42020213391

ABSTRACT

Introduction

Due to overcrowding, personnel shortages, or problematic intravenous (IV) cannulation, acute pain management is often sub-optimal in emergency departments (EDs). The objective of this systematic review and meta-analysis was to evaluate the efficacy and safety of intranasal (IN) ketamine for adult acute pain in the emergency setting.

Methods

We searched and identified studies up to 21 May 2021 via PubMed, Scopus, Web of Science, Cochrane Database, and Google Scholar. The random-effects model with 95% confidence intervals (CIs) was used to estimate mean differences (MDs) and odds ratios (ORs). The I^2 statistic and Cochran's Q test were used to determine heterogeneity.

Results

Seven randomised controlled trials were included with a total of 1760 patients. There was no significant difference in pain scores comparing IN ketamine with IV analgesics or placebo at 5 (MD 0.94, p = 0.26), 15 (MD 0.15, p = 0.74), 25 (MD 0.24, p = 0.62), 30 (MD -0.05, p = 0.87), and 60 (MD -0.42, p = 0.53) minutes. There was also no significant difference in the need for rescue analgesics between IN ketamine and IV analgesics (OR 1.66, 95% CI: 0.57-4.86, p = 0.35, I2 = 70%). Only mild adverse effects were observed in patients who received IN ketamine.

Conclusion

Our results suggest that IN ketamine is non-inferior to IV analgesics and may have a role in acute pain management among adults in the ED.

Trial registration number: PROSPERO CRD42020213391

CHAPTER 1: STUDY PROTOCOL

1.1 BACKGROUND

1.1.1 Description of the condition

Acute pain is one of the most frequent presentations to the emergency departments (ED). Between 2000 and 2010, pain was the leading complaint in 45.4% of the total ED visits, and patients reported pain as a symptom twice as high as those recorded by healthcare professionals (40% vs. 20%) (Chang et al. 2014). A wide range of pain diagnoses is brought to EDs, including acute injuries (30%), infections (14%), abdominal pain (12%), chest discomfort (12%), and others (16%) (Samcam and Papa 2016). The most common pain management challenge in the ED is oligoanalgesia (underuse of analgesics). Despite the availability of a variety of analgesics, pain is nevertheless undertreated (Rupp and Delaney 2004). Inadequate management tends to negatively impact patients' quality of life, physical and mental functions. Underuse of analgesics in the EDs can lead to worsened pain and frequent hospital visits, resulting in an enormous burden of cost. Patients with severe acute pain may develop chronic pain as a consequence of oligoanalgesia (Sinatra 2010).

Emergency staff shortage, limited beds, and inadequate patient monitoring are the critical management issues in overcrowded ED, which necessitate the use of analgesics that are easier to deliver, faster and with fewer adverse effects (Kahsay and Pitkäjärvi 2019). In the ED, delayed pain management is common and usually provided after the patient's clinical assessment. The initial analgesic drug is usually administered after 70 to 90 min of waiting time, and the dosage is often inadequate to relieve pain (Todd et al. 2007, Vazirani and Knott 2012). In addition, difficult intravenous (IV) cannulation delays pain relief in the emergency setting (Schwartz and Charity 2001).

The opioid abuse and addiction problems are rapidly growing in the United States

(U.S.). In 2017, approximately 47,000 people died from opioid overdose in the U.S. (Hedegaard, Miniño and Warner 2018). Opioids are the mainstay of analgesic therapy for moderate to severe pain in the emergency setting. However, patients with hemodynamic instability or potential respiratory and airway compromise requires close monitoring when given opioid. Despite its effectiveness, the available data revealed a strong correlation between opioid prescriptions and opioid-related fatalities. This is due to opioid side effects such as dependence, tolerance, respiratory suppression, and hypotension, especially in situations of opioid overdose (Alexander, Kruszewski and Webster 2012, Campbell 2012). The American College of Emergency Physicians (ACEP) recommends a multimodal approach to acute pain management that incorporates pharmacologic and nonpharmacologic therapies. Unless contraindicated or non-opioid pain refractory, it should start with non-opioids (2017).

1.1.2 Description of the intervention and how the intervention might work

Ketamine has been extensively used for procedural sedation and as an induction agent for rapid sequence intubation (RSI) since its introduction to medicine in the 1960s due to its safe hemodynamic profile (Li and Vlisides 2016). The anesthetic and analgesic effects of ketamine are primarily mediated through non-competitive antagonism of the N-methyl-D-aspartate (NMDA) receptor Ca^{2+} channel pore in the central nervous system (CNS) and spinal cord. It also reduces the presynaptic release of excitatory neurotransmitter (glutamate). Furthermore, ketamine and its metabolites have a ten-fold lower affinity for opioid receptors (μ, δ, and κ receptors) than the NMDA receptor and antagonistic activity for nicotinic, muscarinic, and monoaminergic receptors (Pai and Heining 2007).

Ketamine's effects are dose-dependent, where the analgesic dosage for pain relief

without sedation is about 10–30% of the dissociative sedative dosage. The typical ketamine analgesic dose without sedation is 0.1 to 0.3 mg/kg IV, 0.5 mg/kg intramuscular (IM) and 1 mg/kg intranasal (IN) as compared to 1 to 2 mg/kg IV, 3 to 4 mg/kg IM and 6 to 9 mg/kg IN for the ketamine dissociative sedation dose (Ahern et al. 2015, Hirlinger and Dick 1984, Green et al. 2011). IN ketamine has a bioavailability of 25–50%, and the analgesic effects begin within ten minutes of administration and may last up to 60 min (Hurth et al. 2020, Carr et al. 2004). The mild and transient side effects of IN ketamine are fatigue, dizziness, euphoria, and nausea, which usually does not require treatment (Hurth et al. 2020). IN ketamine is a quick and non-invasive method of drug administration and provides an analgesic effect in acute pain. It might be used in overcrowded EDs and prehospital situations where IV cannulation is not required or difficult (Parvizrad et al. 2017). Moreover, a systematic review of ketamine's analgesic effect on burn injuries in adults found its effectiveness in pain relief and reduced secondary hyperalgesia compared to opioids. The combination of ketamine and morphine treatment reduced the windup phenomenon (McGuinness et al. 2011).

1.1.3 Why it is important to do this review

Ketamine is extensively utilised in adult populations as an adjuvant to opioid pain therapy to reduce opioid use. In addition, ketamine is being studied as a first-line analgesic treatment for acute pain to minimise opioid consumption (Bouida et al. 2020). Recent randomised controlled trials (RCTs) have evaluated IN ketamine's analgesic effectiveness and safety in the adult population.

1.1.4 Objective

To evaluate the efficacy and safety of IN ketamine in the management of acute pain among adults in the emergency department.

1.1.5 Outcomes

Primary outcomes

1. The analgesic efficacy of IN ketamine in pain score reduction
2. The requirement for rescue analgesics

Secondary outcomes

1. The prevalence of the adverse events

1.2 METHODS

1.2.1 Eligibility criteria

Types of studies

Randomised control trials (RCTs) comparing IN ketamine to IV analgesics (morphine, fentanyl, and ketamine) or IN placebo for acute pain management in emergency department.

Types of participants

Adults (age ≥ 15 years old) who presented to ED with acute pain with numeric rating scale (NRS) or visual analogue scale (VAS) ≥ 5.

Types of interventions

Intervention: IN ketamine only

Comparison: IV morphine, IV fentanyl, IV ketamine or IN placebo

Types of outcomes

Pain score reduction, the requirement of rescue analgesia and adverse events.

1.2.2 Search strategies

Electronic searches

We will search the electronic databases of PubMed, Scopus, Google Scholar, Web of Science, and Cochrane Library (from inception to 21 May 2021). We will use the search strategy in Appendix Table S1. We will restrict the publications to English language only.

Searching other resources

We will search the reference list of identified RCTs and review the articles in order to identify the further potential studies to include in the systematic review and meta-analysis (SRMA). We will search for ongoing trials through the World Health Organization's (WHO) International Clinical Studies Registry Platform and ClinicalTrials.gov. We will filter out the duplicate studies by using EndNote X8 software.

1.2.3 Trial Selection

We will screen the titles and abstracts (Y.S.S. and M.A.I.) from the searches and obtain full- test articles when they appear to meet the eligibility criteria. We will assess the eligibility of the trials independently and document the reasons for exclusion. We will resolve the discrepancies between the authors by discussion. We will contact the authors if clarification is needed.

1.2.4 Data extraction

We will extract the data independently (Y.S.S. and M.A.I.) from the full-text reports and supplemental materials. We will extract the following information into a data extraction form:

- Study setting (study design, study size);
- Participant's characteristics (age, sex);
- Causes of pain;
- Intervention details (doses and timing);
- Outcomes of interest, including pain scores pre- and post-intervention, the need for rescue analgesics, and the prevalence of adverse events from each of the eligible study.

We will attempt to contact the corresponding authors of included trials for the missing or incomplete data. We will resolve the disagreements between the authors by discussion.

1.2.5 Risk of bias assessment

We plan to perform publication bias analysis if there are 10 or more studies. We will resolve any disagreements by discussion among authors.

1.2.6 Quality Assessment

We will assess the quality of included RCTs independently (Y.S.S. and M.A.I.) by using the Joanna Briggs Institute (JBI) critical appraisal tool (Moola et al. 2020). Studies will be classified as poor quality (high risk of bias), moderate quality (moderate risk of bias), or

high quality (low risk of bias) if the total score was ≤49%, 50–69%, or ≥70% (Islam et al. 2020, Chia et al. 2021).

1.2.6 Data Synthesis and Analysis

We will calculate the mean differences (MDs) with associated 95% confidence intervals (CIs) for the continuous data of pain score reduction at 5, 10, 15, 20, 25, 30, and 60 min of post-intervention for IN ketamine versus IV analgesics (morphine, fentanyl, or ketamine) or placebo. The subgroup analyses will be carried out based on the comparative drugs. We will compute the odds ratios (ORs) with associated 95% CIs for rescue analgesia and adverse events for the dichotomous data. We will also calculate the prevalence of adverse events with associated 95% CIs. We plan to contact the authors for the unreported outcomes of interest, such as MD or standard deviations. We will use the Review Manager (RevMan) calculator to impute missing data when we could not contact the authors as recommended by the Cochrane handbook (Higgins JPT 2021). We also plan to extract data from figures or graphs using WebPlotDigitizer Software 4.4 version. We will use RevMan version 5.4 and metaprop codes in the meta (version 4.15-1) and metafor (version 2.4-0) packages of R (version 3.6.3) in RStudio (version 1.3.1093) to create all analyses and plots (Viechtbauer 2010).

The random-effects model will be used in all meta-analyses, and we will assess trial heterogeneity by using the I^2 statistic (I^2 > 75% indicating significant heterogeneity). The Cochran's Q test will be employed to assess the significance of the heterogeneity test; a *p*-value of 0.05 indicated significant heterogeneity (Alam et al. 2019, Chang et al. 2021). We will perform sensitivity analysis by excluding the low or moderate quality studies and using a fixed-effects model.

1.3 Contributions of Authors

Conceptualization**:** Y.S.S., M.A.I., T.H.T.K. and J.N.

Methodology**:** Y.S.S. and M.A.I.

Software**:** Y.S.S. and M.A.I.

Validation**:** Y.S.S. and M.A.I.

Formal analysis**:** Y.S.S. and M.A.I.

Investigation**:** Y.S.S. and M.A.I.

Resources**:** Y.S.S. and M.A.I.

Data curation**:** Y.S.S. and M.A.I.

Writing—original draft preparation**:** Y.S.S.

Writing—review and editing**:** M.A.I., T.H.T.K., J.N. and A.A.

1.4 APPENDIX

1.4.1 Search Strategy

Table S1. Search strategies

Databases	Search strategies
PubMed	((Ketamine[Title/Abstract]) AND (pain[Title/Abstract])) AND (emergency[Title/Abstract])
Scopus	TITLE(Ketamine) AND TITLE-ABS-KEY(pain) AND TITLE-ABS-KEY(emergency)
Google Scholar	allintitle: ketamine acute pain
Web of Science	TI=(Ketamine) AND TI=(pain) AND TI=(emergency)
Cochrane Database	Record title: Ketamine AND pain AND emergency

1.4.2 Characteristics of Included Studies

Study ID	Country	Sample Size	Age In Years	Causes Of Acute Pain	Pain Scale Used	Intervention	Comparator	Outcome

1.4.3 Comparison Between Intervention and Control for A Particular Outcome

Outcome:								
Study or Subgroup	Intervention			Control			Weight	Mean Difference
	Mean	SD	n	Mean	SD	n		IV, Random, 95% CI
Total 95% CI								
Heterogeneity: Tau^2= ; Chi^2= , df= (P=); I^2= %								
Test for overall effect: Z= (P=)								
Test for subgroup difference: Chi^2= , df= (P=); I^2= %								

Outcome:							
Study or Subgroup	Intervention		Control		Weight	Odds Ratio	
	Events	Total	Events	Total		M-H, Random, 95%CI	
Total 95% CI							
Total events							
Heterogeneity: Tau^2=, Chi^2= , df= (P=); I^2=%							
Test for overall effect: Z= (P=)							

Adverse Effects	Prevalence 95% CIs	Number of Studies Analysed	Total Numbers of Patients	Heterogeneity		Odds Ratio 95% CI	p-Value	Heterogeneity	
				I^2	p-Value			I^2	P-Value

Study ID	Cases	Total	Prevalence	95% CI
Random effects model Heterogeneity: I^2= , τ^2= , χ= (p=)				

1.4.4 PRISMA Flow Diagram

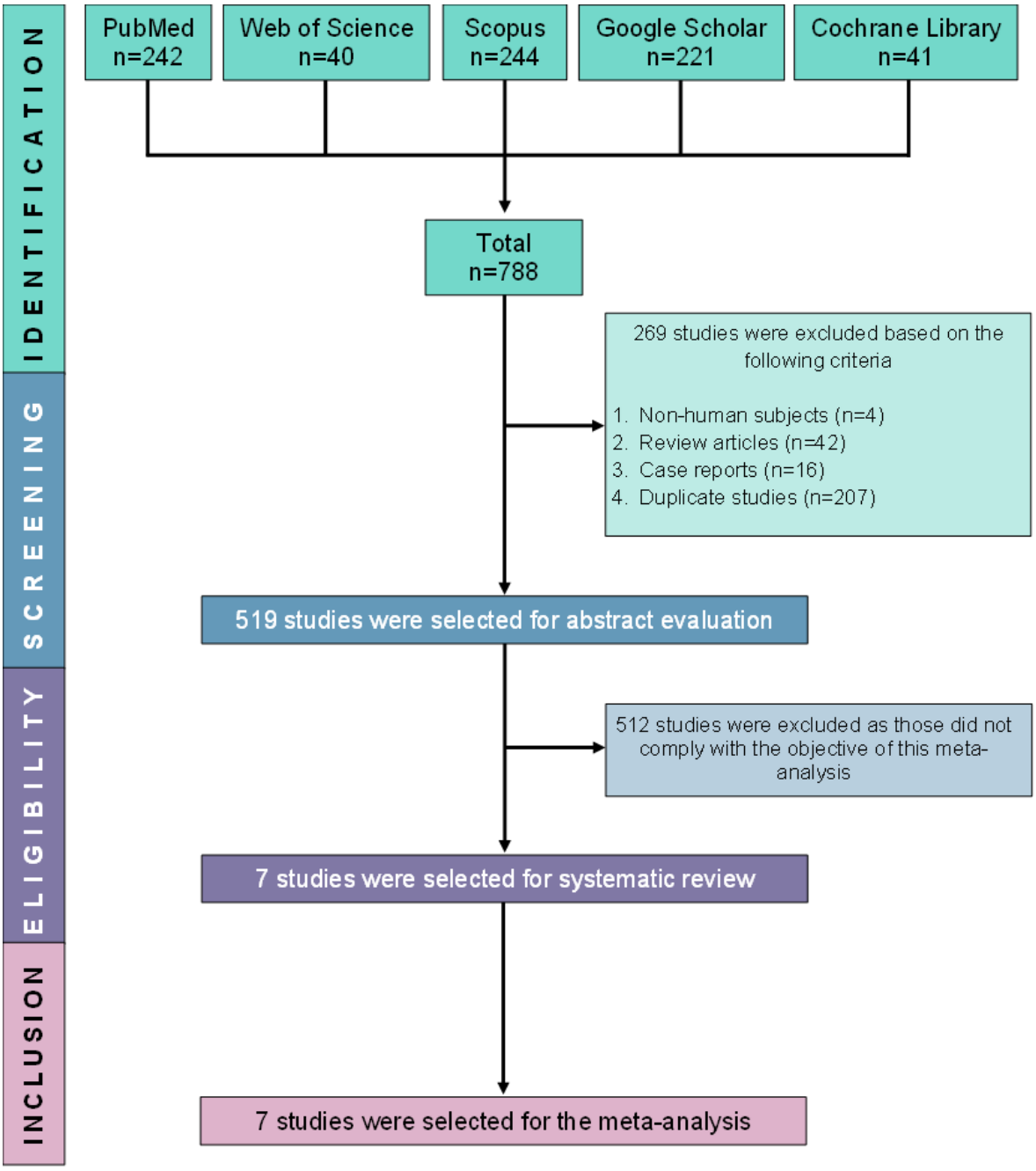

Figure 1. PRISMA flow diagram of study selection

1.5 RELEVANT TRIALS

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1.7 ETHICAL APPROVAL LETTER

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)

Human Research Ethics Committee USM (HREC)

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12th January 2021

Dr. Seak Yee Sin
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16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/21010002
Protocol Title : Efficacy and Safety of Intranasal Ketamine for Acute Pain in an Emergency Setting: A Systematic Review and Meta-Analysis.

Dear Dr.,

We wish to inform you that the Jawatankuasa Etika Penyelidikan (Manusia), JEPeM USM has reviewed your study protocol entitled, **"Efficacy and Safety of Intranasal Ketamine for Acute Pain in an Emergency Setting: A Systematic Review and Meta-Analysis"**.

Upon review of study protocol, the committee decided that this project can be exempted from ethical review. Should you require any additional information, kindly please contact JEPeM USM Secretariat at 09-7672354/2352 and email at bazlan@usm.my/ctfatihah@usm.my.

Thank you.

"ENSURING A SUSTAINABLE TOMORROW"

Very truly yours,

PROF. DR. HANS AMIN VAN ROSTENBERGHE
Chairperson
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia

CHAPTER 2.0: MANUSCRIPT

2.1 TITLE PAGE

EFFICACY AND SAFETY OF INTRANASAL KETAMINE FOR ACUTE PAIN MANAGEMENT IN THE EMERGENCY SETTING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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2.2 ABSTRACT

Introduction

Due to overcrowding, personnel shortages, or problematic intravenous (IV) cannulation, acute pain management is often sub-optimal in emergency departments (EDs). The objective of this systematic review and meta-analysis was to evaluate the efficacy and safety of intranasal (IN) ketamine for adult acute pain in the emergency setting.

Methods

We searched and identified studies up to 21 May 2021 via PubMed, Scopus, Web of Science, Cochrane Database, and Google Scholar. The random-effects model with 95% confidence intervals (CIs) was used to estimate mean differences (MDs) and odds ratios (ORs). The I2 statistic and Cochran's Q test were used to determine heterogeneity.

Results

Seven randomised controlled trials were included with a total of 1760 patients. There was no significant difference in pain scores comparing IN ketamine with IV analgesics or placebo at 5 (MD 0.94, p = 0.26), 15 (MD 0.15, p = 0.74), 25 (MD 0.24, p = 0.62), 30 (MD -0.05, p = 0.87), and 60 (MD -0.42, p = 0.53) minutes. There was also no significant difference in the need for rescue analgesics between IN ketamine and IV analgesics (OR 1.66, 95% CI: 0.57-4.86, p = 0.35, I2 = 70%). Only mild adverse effects were observed in patients who received IN ketamine.

Conclusion

Our results suggest that IN ketamine is non-inferior to IV analgesics and may have a role in acute pain management among adults in the ED.

Trial registration number: PROSPERO CRD42020213391

2.3 INTRODUCTION

Acute pain is one of the most frequent presentations to the emergency departments (ED). Between 2000 and 2010, pain was the leading complaint in 45.4% of the total ED visits, and patients reported pain as a symptom twice as high as those recorded by healthcare professionals (40% vs. 20%).[1] A wide range of pain diagnoses is brought to EDs, including acute injuries (30%), infections (14%), abdominal pain (12%), chest discomfort (12%), and others (16%).[2] The most common pain management challenge in the ED is oligoanalgesia (underuse of analgesics). Despite the availability of a variety of analgesics, pain is nevertheless undertreated.[3] Inadequate management tends to negatively impact patients' quality of life, physical and mental functions. Underuse of analgesics in the EDs can lead to worsened pain and frequent hospital visits, resulting in an enormous burden of cost. Patients with severe acute pain may develop chronic pain as a consequence of oligoanalgesia.[4]

Emergency staff shortage, limited beds, and inadequate patient monitoring are the critical management issues in overcrowded ED, which necessitate the use of analgesics that are easier to deliver, faster and with fewer adverse effects.[5] In the ED, delayed pain management is common and usually provided after the patient's clinical assessment. The initial analgesic drug is usually administered after 70 to 90 min of waiting time, and the dosage is often inadequate to relieve pain.[6,7] In addition, difficult intravenous (IV) cannulation delays pain relief in the emergency setting.[8]

The opioid abuse and addiction problems are rapidly growing in the United States (U.S.). In 2017, approximately 47,000 people died from opioid overdose in the U.S.[9] Opioids are the mainstay of analgesic therapy for moderate to severe pain in the emergency setting. However, patients with hemodynamic instability or potential respiratory and airway compromise requires close monitoring when given opioid. Despite its effectiveness, the

available data revealed a strong correlation between opioid prescriptions and opioid-related fatalities. This is due to opioid side effects such as dependence, tolerance, respiratory suppression, and hypotension, especially in situations of opioid overdose.[10,11] The American College of Emergency Physicians (ACEP) recommends a multimodal approach to acute pain management that incorporates pharmacologic and nonpharmacologic therapies. Unless contraindicated or non-opioid pain refractory, it should start with non-opioids.[12]

Ketamine has been extensively used for procedural sedation and as an induction agent for rapid sequence intubation (RSI) since its introduction to medicine in the 1960s due to its safe hemodynamic profile.[13] The anesthetic and analgesic effects of ketamine are primarily mediated through non-competitive antagonism of the N-methyl-D-aspartate (NMDA) receptor Ca^{2+} channel pore in the central nervous system (CNS) and spinal cord. It also reduces the presynaptic release of excitatory neurotransmitter (glutamate). Furthermore, ketamine and its metabolites have a ten-fold lower affinity for opioid receptors (μ, δ, and κ receptors) than the NMDA receptor and antagonistic activity for nicotinic, muscarinic, and monoaminergic receptors.[14]

Ketamine's effects are dose-dependent, where the analgesic dosage for pain relief without sedation is about 10–30% of the dissociative sedative dosage. The typical ketamine analgesic dose without sedation is 0.1 to 0.3 mg/kg IV, 0.5 mg/kg intramuscular (IM) and 1 mg/kg intranasal (IN) as compared to 1 to 2 mg/kg IV, 3 to 4 mg/kg IM and 6 to 9 mg/kg IN for the ketamine dissociative sedation dose.[15-17] IN ketamine has a bioavailability of 25–50%, and the analgesic effects begin within ten minutes of administration and may last up to 60 min.[18,19] The mild and transient side effects of IN ketamine are fatigue, dizziness, euphoria, and nausea, which usually does not require treatment.[18] IN ketamine is a quick and non-invasive method of drug administration and provides an analgesic effect in acute pain. It

might be used in overcrowded EDs and prehospital situations where IV cannulation is not required or difficult.[20] Moreover, a systematic review of ketamine's analgesic effect on burn injuries in adults found its effectiveness in pain relief and reduced secondary hyperalgesia compared to opioids. The combination of ketamine and morphine treatment reduced the windup phenomenon.[21]

Ketamine is extensively utilised in adult populations as an adjuvant to opioid pain therapy to reduce opioid use. In addition, ketamine is being studied as a first-line analgesic treatment for acute pain to minimise opioid consumption.[22] Recent randomised controlled trials (RCTs) have evaluated IN ketamine's analgesic effectiveness and safety in the adult population. Therefore, the objective of this systematic review and meta-analysis (SRMA) was to evaluate the efficacy and safety of IN ketamine in the management of acute pain among adults in the emergency department. We evaluated the efficacy of IN ketamine by assessing the pain score reduction and the requirement for rescue analgesics. In addition, the prevalence of adverse events was analyzed to assess the safety of IN ketamine in acute pain management.

2.4 METHODS

We conducted an SRMA to assess the efficacy and safety of IN ketamine as an analgesic agent for acute pain management among adults in ED. This SRMA was conducted in accordance with the protocol registered with PROSPERO (CRD42020213391). The methodology and reporting were constructed based on the updated guideline of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline.[23]

2.4.1 Data Sources and Searches

Studies published from inception to 21 May 2021 were searched and identified via electronic databases of PubMed, Scopus, Google Scholar, Web of Science, and Cochrane Library. Table S1 summarises the search strategy. We searched the RCT reference lists for further potential studies to include in the SRMA. In addition, the World Health Organization's (WHO) International Clinical Studies Registry Platform and ClinicalTrials.gov were used to search for completed and ongoing trials. Duplicate studies were filtered out using EndNote X8 software.

2.4.2 Study Selection

Only RCTs comparing IN ketamine to IV analgesics (morphine, fentanyl, and ketamine) or IN placebo in acute pain management were included. The SRMA's inclusion criteria were as follows: (1) RCT; (2) population: adults (age ≥ 15 years old) who presented to ED with acute pain with numeric rating scale (NRS) or visual analogue scale (VAS) ≥ 5; (3) intervention: IN ketamine only; (4) comparison: IV morphine, IV fentanyl, IV ketamine or IN placebo; (5) outcomes: pain score reduction, the requirement of rescue analgesia and adverse events. We restricted the publications to the English language only. Ketamine's analgesic effects on perioperative pain (i.e., subacute pain) following anesthesia, cancer-related pain, and other non-acute pain were eliminated from the study. Studies performed in non-ED settings, such as postoperative or prehospital, were also excluded. We excluded studies where IN ketamine was given as a combination therapy with other analgesics such as inhaled nitrous oxide or IV morphine. Studies that used higher dosage for procedural sedation or IV, IM, oral, or topical routes as ketamine intervention were not considered. Our SRMA

eliminated studies that compared IN ketamine to analgesics administered orally, topically, IM, or IN. The titles and abstracts were screened, and eligible RCTs were selected by two authors independently (Y.S.S. and M.A.I.). We gathered full-text copies of the relevant articles to determine if they met the inclusion criteria. Discrepancies between the authors were resolved through discussions.

2.4.3 Outcome Measures

Our primary outcome was to evaluate the analgesic efficacy of IN ketamine in pain score reduction using validated pain scales (NRS or VAS) from baseline to post-intervention and the requirement for rescue analgesics. The following time points were included: 5, 10, 15, 20, 25, 30, and 60 min. We analysed the prevalence of the adverse events, such as dizziness, nausea, vomiting, agitation, difficulty in concentration, confusion, emergence phenomenon, dry mouth, fatigue, disorientation, drowsiness, euphoria, headache, and hypotension as the secondary outcomes for evaluating the safety of IN ketamine.

2.4.4 Data Extraction and Quality Assessment

The data were extracted independently by two authors (Y.S.S. and M.A.I.) from the full-text reports and supplemental materials. We extracted the following information into a data extraction form: study design, study size, study population, causes of pain, intervention details (doses and timing), outcomes of interest, including pain scores pre- and post-intervention, the need for rescue analgesics, and the prevalence of adverse events from each of the eligible study. We attempted contacting the corresponding authors of included trials that had missing or incomplete data. Disagreements were resolved through the discussion