European Review for Medical and Pharmacological Sciences 2021; 25: 3286-3295

Efficacy of intranasal ketamine for acute pain management in adults: a systematic review and meta-analysis

X. LI[1], G.-C. HUA[2], F. PENG[1]

[1]Department of Pharmacy, Zaozhuang Municipal Hospital, Zaozhuang, Shandong Province, P.R. China
[2]Department of Pain, Zaozhuang Municipal Hospital, Zaozhuang, Shandong Province, P.R. China

Abstract. – OBJECTIVE: This study aimed to compare the efficacy of intranasal (IN) ketamine for pain control with placebo and other analgesics in an emergency setting.

MATERIALS AND METHODS: Electronic databases of PubMed, Embase, and CENTRAL were searched for randomized controlled trials (RCTs) comparing IN ketamine with placebo or other analgesics up to 1st January 2021. Studies were to be conducted on adults and in an emergency setting. Pain outcomes and adverse events were compared.

RESULTS: Seven RCTs were included. Three compared IN ketamine with placebo while others with opioids. Comparing IN ketamine with opioids, the pooled analysis demonstrated no significant difference in pain scores between the two groups at 15 minutes but better pain reduction with opioids at 30 minutes. Comparing IN ketamine with placebo, our analysis demonstrated a non-significant difference but a tendency for better pain relief with IN ketamine at 15 minutes and 60 minutes. Pain scores at 30 minutes were, however, significantly lower with IN ketamine as compared to placebo. The need for rescue analgesics was significantly lower with IN ketamine as compared to placebo. There was no significant difference in the incidence of dizziness and nausea/vomiting between IN ketamine and opioids. As compared to placebo, IN ketamine was associated with an increased incidence of dizziness but not nausea/vomiting. Emergence reactions were significantly increased with IN ketamine as compared to opioids and placebo.

CONCLUSIONS: There may be a role of IN ketamine for acute pain management in adults in an emergency setting. There is a tendency for better pain control with IN ketamine as compared to control and the possibility of similar efficacy of IN ketamine as compared to opioids. However, the results are not unequivocal and are limited by the low number of studies in literature and limited pain indications studied. Further RCTs are required to strengthen the evidence.

Key Words:
Ketamine, Intranasal, Pain, Emergency, Trauma, Renal colic.

Introduction

Pain is the most common presenting complaint in the emergency department (ED)[1]and oligoanalgesia in this setting is known to be common. The Joint Commission on Accreditation of Healthcare Organizations has revised standards for pain management; however, the impact of these regulatory changes on ED pain management practice is unknown. This prospective, multicenter study assessed the current state of ED pain management practice. After informed consent, patients aged 8 years and older with presenting pain intensity scores of 4 or greater on an 11-point numerical rating scale completed structured interviews, and their medical records were abstracted. Eight hundred forty-two patients at 20 US and Canadian hospitals participated. On arrival, pain intensity was severe (median, 8/10. Acute management of pain in such a setting is an essential component of patient satisfaction and care. One of the most commonly prescribed drugs in the ED for pain management are opioids[2]. However, due to increased misuse of opioids, there has been a trend of judicious opioid prescription amongst clinicians with a need for an alternative non-opioid analgesic[3]. While a short course of opioids is unlikely to cause drug addiction by itself, concerns have been raised that opioid prescription in the ED may increase recurrent opioid use in the future and it may act as a potential trigger for substance abuse disorders[4,5]particularly in short courses, as is typical of the emergency department (ED. Also, a specific cohort of patients like the elderly, patients with a history of drug ad-

Corresponding Author: Fang Peng, MD; e-mail: pf_1986@126.com

diction, alcohol dependence, and chronic opioid users may benefit from an alternative non-opioid drug that is equally effective and safe to use in an emergency setting[6]the global increase in aged population will pose a challenge for emergency services. In this study we examined the burden caused to emergency health care by the aged population. Methods: Consecutive patients aged 80 years or over visiting a high-volume, collaborative emergency department (ED.

One such non-opioid alternative is ketamine. The drug is a N-methyl-D-aspartate (NMDA) receptor antagonist that acts on the central nervous system and has anesthetic and analgesic properties[7]. Ketamine has been widely used for controlling prehospital agitation, preprocedural sedation, and intubations in an emergency setting[8-10]critical care, and the prehospital setting. Traditional rapid sequence intubation (RSI. The drug is commonly administered via intravenous (IV) route and is an effective alternative to opioids for pain control in the ED[11]. However, sometimes IV catheter placement can be difficult in a pre-hospital, mass casualty, or even in a routine ED setting, thereby hindering pain management (Schwartz). In this context, intranasal (IN) administration of analgesics is easy and safe in the ED, especially with opioids[12,13]. Recent studies[10,14] suggest that IN formulation of ketamine may also be effective in the ED. In a meta-analysis published in 2020, Oliveira et al[14] have demonstrated that IN ketamine is an effective alternative to IN fentanyl for acute pain relief in children. However, to the best of our knowledge, no study has attempted to synthesize evidence on the efficacy of IN ketamine for adults in the ED. Thus, the current study aimed to perform a systematic literature search for studies comparing IN ketamine with placebo or other analgesics for acute pain relief in adults in an emergency setting and conduct a quantitative analysis to present high-level evidence.

Material and Methods

Search Strategy

The review was conducted following the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[15] and the Cochrane Handbook for Systematic Reviews of Intervention[16]. The review protocol was not registered on PROSPERO. Articles on the subject of the review were searched in the electronic databases of PubMed, Embase, and CENTRAL up to 1st January 2021. Databases were searched from inception and without any language restriction. We used the following keywords for the literature search: "ketamine", "intranasal", "pain", and "emergency". Table I depicts the search strategy of the review. Two reviewers carried out the electronic search independent of each other. The primary search results were assessed initially by their titles and abstracts to identify citations requiring full-text analysis. The full texts of the articles were reviewed by the two reviewers independently based on the inclusion and exclusion criteria. Any disagreements were resolved by discussion. Furthermore, we also hand-searched the bibliography of included studies for any missed references.

Table I. Search strategy.

Query	Search details
((ketamine) AND (pain)) AND (emergency)	("esketamine"[Supplementary Concept] OR "esketamine"[All Fields] OR "ketamine"[All Fields] OR "ketamine"[MeSH Terms] OR "ketamin"[All Fields] OR "ketamine s"[All Fields] OR "ketamines" [All Fields]) AND ("pain"[MeSH Terms] OR "pain"[All Fields]) AND ("emerge"[All Fields] OR "emerged"[All Fields] OR "emergence" [All Fields] OR "emergences"[All Fields] OR "emergencies" [MeSH Terms] OR "emergencies"[All Fields] OR "emergency" [All Fields] OR "emergent"[All Fields] OR "emergently"[All Fields] OR "emergents"[All Fields] OR "emerges"[All Fields] OR "emerging" [All Fields])
(ketamine) AND (intranasal)	("esketamine"[Supplementary Concept] OR "esketamine"[All Fields] OR "ketamine"[All Fields] OR "ketamine"[MeSH Terms] OR "ketamin"[All Fields] OR "ketamine s"[All Fields] OR "ketamines"[All Fields]) AND ("intranasal"[All Fields] OR "intranasally"[All Fields])

Inclusion Criteria

The PICOS (Population, Intervention, Comparison, Outcome, and Study design) guide was used to include studies. The following criteria were used for each domain:

Population: Adult patients (>15 years of age) with pain of any kind in an emergency or pre-emergency setting.
Intervention: IN ketamine.
Comparison: Placebo or any other analgesic drug.
Outcomes: Pain scores and/or need for analgesics, adverse events.
Study design: Randomised controlled trials (RCTs).

Exclusion criteria were: (1) Studies using ketamine in a non-emergency setting (2) Use of any other route of administration of ketamine (3) Use of ketamine for sedation and not pain relief (4) Studies on pediatric patients (5) Non-RCTs, retrospective studies, animal studies, and review articles.

Data Extraction

A data extraction sheet was prepared for extracting data from the included studies. Two reviewers extracted data independently. Data regarding the first author, publication year, study location, patient population, sample size, mean age, study and control drug protocol, use of any other analgesics, and study outcomes were extracted. The outcomes of interest were pain scores at 15, 30, and 60 minutes after the intervention, need for other analgesics, and adverse events. The corresponding author was contacted via email in case of any missing data. Descriptive analysis was carried out If the study could not be included in the meta-analysis.

Risk of Bias Assessment

The Cochrane Collaboration's risk of bias assessment tool-2 was used to assess study quality by two reviewers independently[16]. The following seven domains were used for quality assessment: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Any disagreements were resolved by discussion. The certainty of the evidence was assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool using the GRADEpro GDT software [GRADEpro Guideline Development Tool. McMaster University, 2020 (developed by Evidence Prime, Inc.)].

Statistical Analysis

"Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) was used for the meta-analysis. Change in pain scores on a 10-point Visual Analog Scale was summarized using Mean Difference (MD) with 95% confidence intervals (CI). For studies reporting data only in graphical format, Engauge Digitizer Version 12.1 was used to extract data. In the case of studies not reporting the change in pain scores, it was calculated from baseline and final pain scores by methods recommended by Cochrane[16]. Median and interquartile range data was converted into mean and standard deviation (SD) when required using the method of Wan et al[17]. Need for analgesics and adverse events were summarized using odds ratios (OR) with 95% CI. Sub-group analyses were carried out based on the comparative drug. The random-effects model was used for all the meta-analyses. Heterogeneity was assessed using the I^2 statistic. I^2 values of 25-50% represented low, values of 50-75% medium, and more than 75% represented substantial heterogeneity. Due to the inclusion of fewer than 10 studies in the review, funnel plots were not used to assess publication bias[16].

Results

The study flow-chart is presented in Figure 1. A total of seven RCTs fulfilled the inclusion criteria[18-24] (Table II). The majority of studies were conducted in Iran. The study population consisted of renal colic patients in three studies[22-24], traumatic pain in another three[18,20,21] while in one study19 all cases of acute pain were included. One study19 was conducted in a pre-ED setting, while all others were conducted in the ED. The majority of studies used 1 mg/kg of IN ketamine, one used 0.5-1 mg/kg[19] while a fixed dose of 25 mg was used in another trial[20]. Three studies[18-20] compared IN ketamine with placebo while the remaining compared it with opioids[21-24]. The smallest sample size was 20 patients in each group[24] while the largest study[20] included around 550 patients per arm.

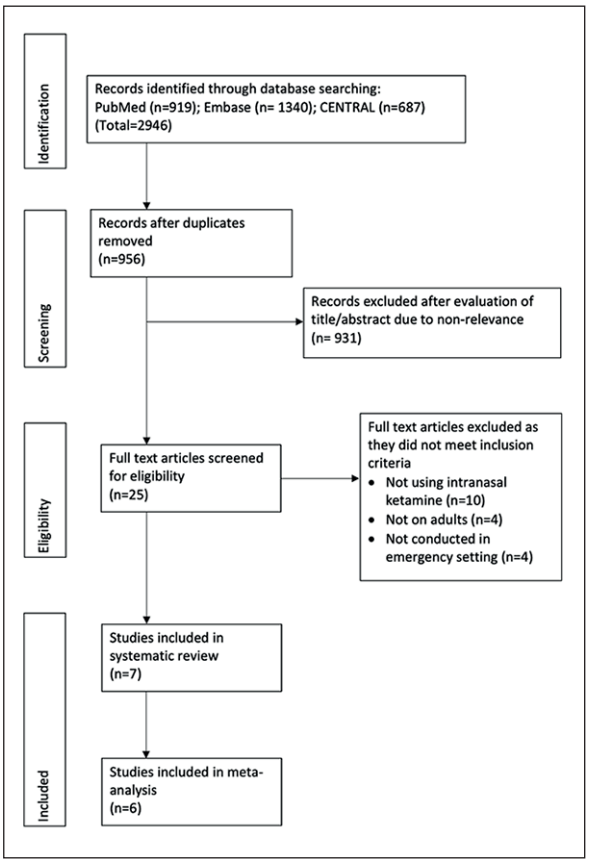

Figure 1. Study flow-chart.

Pain Outcomes

Pouraghaei et al[23] reported only mean but not SD of pain scores. Attempts to retrieve data from the corresponding author were unsuccessful. In this study, the authors comparing IN ketamine with IV morphine in a population of renal colics reported no statistically significant difference in mean pain scores (on a 10-point numerical rating scale) at baseline (8.24 *vs.* 8.11), 15 minutes (5.22 *vs.* 4.85), 30 minutes (2.98 *vs.* 2.97), and 60 minutes (1.67 *vs.* 1.53) between ketamine and morphine groups respectively. Excluding the study of Pouraghaei et al[23], a meta-analysis was conducted for the remaining trials. The certainty of evidence-based on GRADE for the meta-analysis is presented in **Supplementary Table I**.

On pooled analysis of three studies comparing IN ketamine with opioids, we found no statistically significant difference in pain scores between the two groups at 15 minutes (MD: 0.35 95% CI: -0.86, 1.56 I^2=88% p=0.57) (Certainty of evidence: moderate) (Figure 2), but better pain reduction with opioids at 30 minutes (MD: 1.09 95% CI: 0.06, 2.13 I^2=83% p=0.04) (Certainty of evidence: low) (Figure 3). The single study reporting pain data at 60 minutes reported no significant difference between the two groups (MD: -0.90, 95% CI: -2.43, 0.63 I^2=not applicable p=0.25) (Certainty of evidence: very low) (Figure 4).

Meta-analysis of data from two studies comparing IN ketamine with placebo demonstrated a non-significant difference but tendency of better pain relief with IN ketamine at 15 minutes (MD: -0.90 95% CI: -2.34, 0.54 I^2=94% p=0.22) (Certainty of evidence: moderate) (Figure 2) and 60 minutes (MD: -1.47 95% CI: -3.04, 0.10 I^2=71% p=0.07) (Certainty of evidence: moderate) (Figure 4). Pain scores at 30 minutes were, however, significantly lower with IN ketamine as compared to placebo (MD: -0.82 95% CI: -1.43, -0.20 I^2=64% p=0.009) (Certainty of evidence: high) (Figure 3).

Data on the need for rescue analgesics was reported only by three studies. The single study comparing IN ketamine with opioids reported increased demand for rescue analgesics in the ketamine group (OR: 4.69 95% CI: 1.75, 12.60 I^2=not applicable p=0.02) (Certainty of evidence: low) (Figure 5). In the two studies comparing IN ketamine with placebo, the demand for rescue analgesics was significantly lower with ketamine (OR: 0.36 95% CI: 0.16, 0.80 I^2=66% p=0.01) (Certainty of evidence: high) (Figure 5).

Adverse Events

Data on the total number of patients experiencing adverse events were not reported by majority studies, hence, a meta-analysis for the same could not be conducted. Instead, a pooled analysis was conducted for the most common adverse events reported, i.e., dizziness, nausea/vomiting, and emergence reactions (delirium, disorientation, hallucinations, etc.). Comparing IN ketamine with opioids, our analysis revealed no significant difference in the incidence of dizziness (OR: 1.78 95% CI: 0.54, 5.93 I^2=43% p=0.34) (Certainty of evidence: low) (**Supplementary Figure 1**) and nausea/vomiting (OR: 1.47 95% CI: 0.67, 3.20 I^2=0% p=0.33) (Certainty of evidence: moderate) (**Supplementary Figure 2**) between the two groups. However, the incidence of emergence reactions was significantly increased with IN ketamine (OR: 5.67 95% CI: 1.59, 20.24 I^2=8% p=0.008) (Certainty of evidence: moderate) (**Supplementary Figure 3**).

Table II. Characteristics of included studies.

Study	Location	Study population	Study drug protocol	Control drug protocol	Sample size	Mean age	Other analgesics	Study conclusion
Pouraghaei 2020[23]	Iran	Renal colic	1 mg/kg IN ketamine plus 1 ml of IV saline	0.1 mg/kg of IV morphine plus four puffs of IN saline	S: 95 C: 89	39.4 ± 3.7 41.3 ± 5.2	NR	IN ketamine was equally effective as IV morphine for pain control
Bouida 2020[20]	Tunisia	Acute trau-matic pain	25 mg of IN ketamine	IN placebo	S: 552 C: 550	37.7± 12.7 36.6 ± 12.9	Recue analgesics: IV morphine if VAS ≥ 70, SC tramadol if VAS 51-69, PCM or NSAID if VAS between 30-50	IN ketamine was associated with de-crease in analgesic use
Mozafari 2019[22]	Iran	Renal colic	1 mg/kg IN ketamine	1 µg/kg of IV fentanyl	S: 65 C: 65	36.9 ± 10.6 (combined)	Recue analgesia: IV morphine after 30 mins if VAS > 3	IN ketamine was less effective than IV fentanyl
Andolfatto 2019[19]	Canada	Acute pain	0.5-1 mg/kg IN ketamine	IN saline	S: 60 C: 60	NR	Nitrous oxide for all patients concurrent with study drugs	IN ketamine was associated with significant reduction in pain relief
Mohammadshahi 2018[18]	Iran	Acute traumatic pain	1 mg/kg IN ketamine	IN placebo	S: 40 C: 40	31.4 ± 10.7 31.8 ± 12.1	IV morphine for all patients. Rescue analgesic: IV morphine after 10 min as per patient demand	IN ketamine was associated with decrease in analgesic use
Shimonovich 2018[21]	Israel	Acute traumatic pain	1 mg/kg IN ketamine	0.1 mg/kg of IV morphine	S: 24 C: 24	37.9 ± NR 42.9 ± NR	NR	IN ketamine was equally effective as IV morphine for pain control
Farnia 2016[24]	Iran	Renal colic	1 mg/kg IN ketamine plus 1 ml of placebo	0.1 mg/kg of IV morphine plus IN placebo	S: 20 C: 20	39.3 ± 10.8 34.8 ± 11.7	Recue analgesia: IV fentanyl after 30 mins	IN ketamine was equally effective as IV morphine for pain control but after 10 mins

IN, intranasal; IV, intravenous; SC, subcutaneous; S, study; C, control; VAS, visual analog scale; NR, not reported; PCM, paracetamol; NSAID, non-steroidal anti-inflammatory drug.

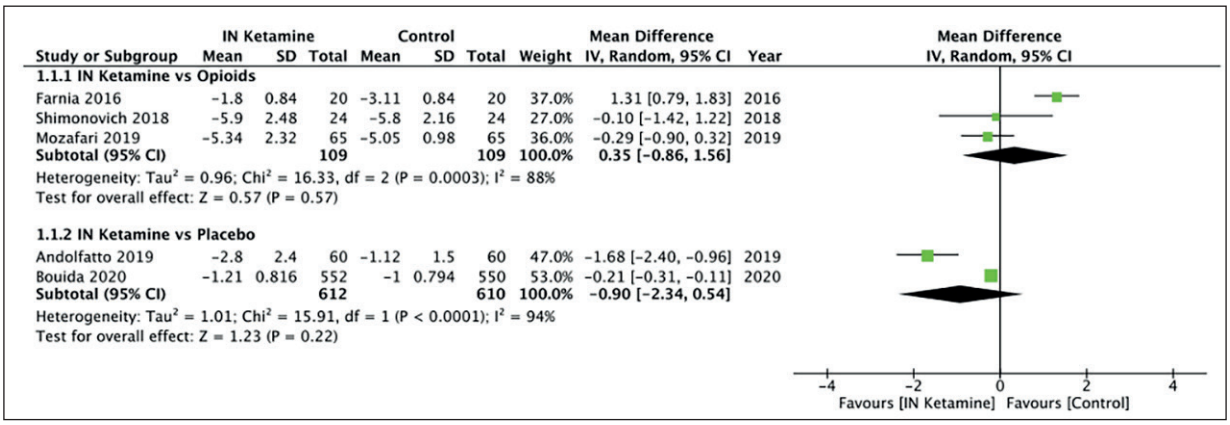

Figure 2. Meta-analysis of changed in pain scores at 15 minutes with sub-group analysis based on comparator drug.

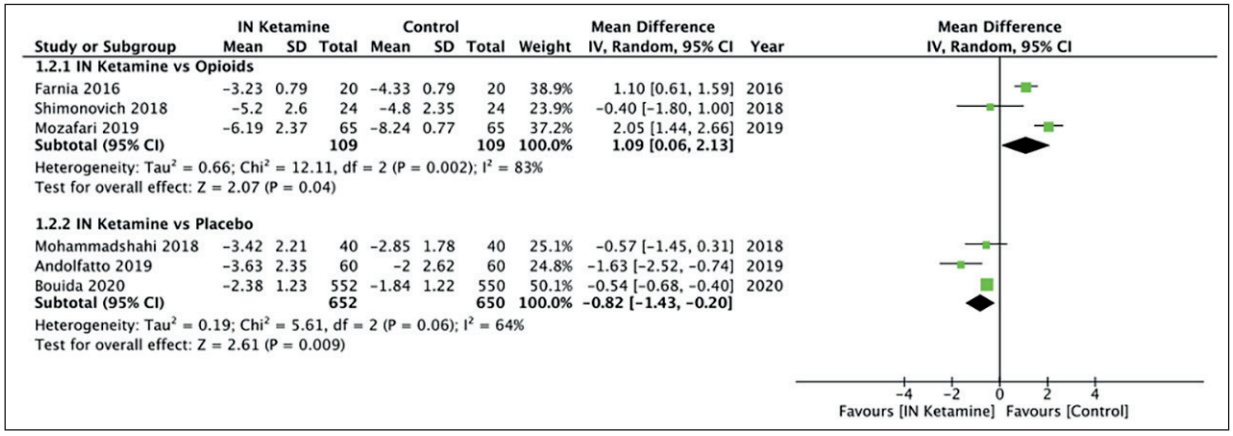

Figure 3. Meta-analysis of changed in pain scores at 30 minutes with sub-group analysis based on comparator drug.

Comparing IN ketamine with placebo, ketamine was associated with significantly increased incidence of dizziness (OR: 1.84 95% CI: 1.35, 2.51 I^2=0% p=0.001) (Certainty of evidence: high) (**Supplementary Figure 1**) and emergence reaction (OR: 10.64 95% CI: 4.55, 24.90 I^2=0% p<0.00001) (Certainty of evidence: high) (**Supplementary Figure 3**), but no difference was noted in the incidence of nausea/vomiting (OR: 1.42 95% CI: 0.75, 2.69 I^2=33% p=0.28) (Certainty of evidence: moderate) (**Supplementary Figure 2**).

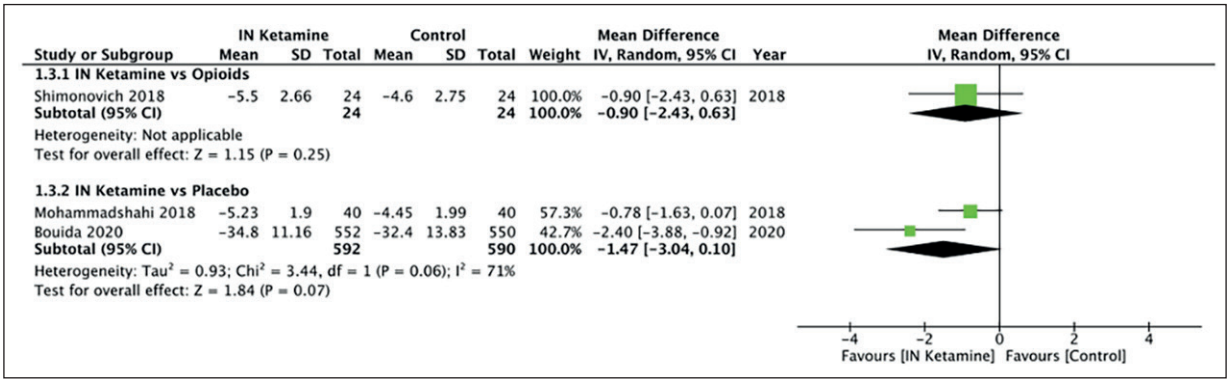

Figure 4. Meta-analysis of changed in pain scores at 60 minutes with sub-group analysis based on comparator drug.

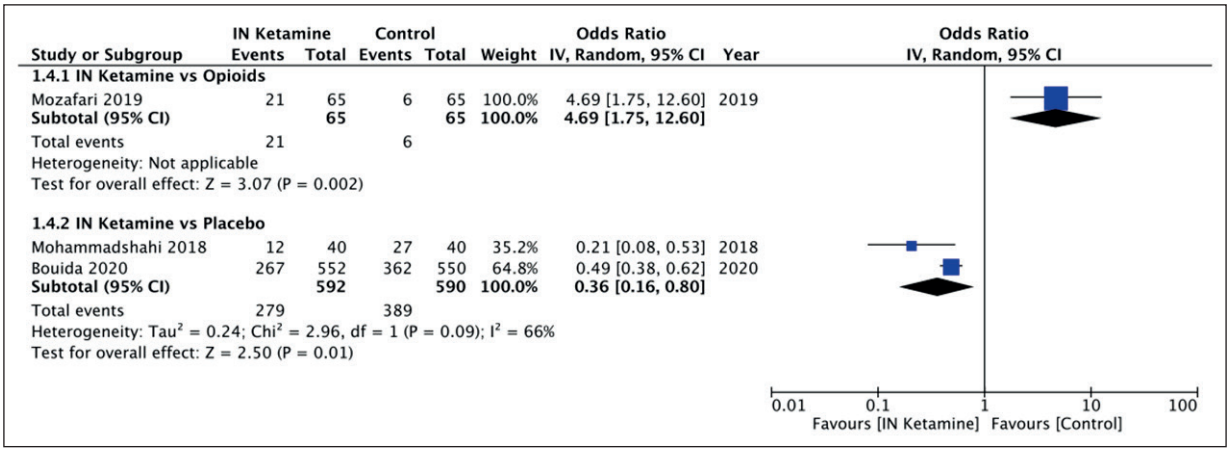

Figure 5. Meta-analysis of need for rescue analgesics with sub-group analysis based on comparator drug.

Risk of Bias

The risk of bias summary of the included studies as per the authors is presented in **Supplementary Figure 4**. The majority were high-quality trials. Shimonovich et al[21] conducted an open-label trial without blinding. Selective reporting was noted in the study of Pouraghaei et al[23].

Discussion

Due to the long history of use of ketamine in the ED for intubations and sedations, emergency physicians are well familiar with the drug[25]. However, only recently the drug has been under immense research for its analgesic properties[11,26]. According to a 2017 policy statement by the American College of Emergency Physicians, management of acute pain in the ED should begin with a non-opioid drug[27]. The document also suggests that low-dose-ketamine (LDK) is an alternative drug that can be used alone or with other agents for acute pain relief in an emergency setting. Such guidelines indicate the importance of having an effective and safe non-opioid alternative for acute pain management in the ED. Furthermore, in light of growing concerns of the opioid epidemic[28]estimate trends in opioid prescribing by site of care (ED, office-based, and inpatient, establishing the efficacy of such non-opioid alternatives is extremely essential to provide confidence to ED clinicians for their routine prescription in daily practice.

The efficacy of IV LDK vis-à-vis IV morphine for acute pain management in the ED has been recently reviewed by Balzer et al[26]. In their meta-analysis of eight RCTs, the authors found no statistically significant difference in the pain scores between LDK and morphine in the first 60 minutes of drug administration with only a slight difference in pain scores favoring morphine at 60 minutes. Thus, while the efficacy of IV ketamine has been established, our study provides evidence on the analgesic effect of IN ketamine compared to placebo as well as opioids. On analysis of a limited number of trials, our results demonstrated no difference in pain scores between IN ketamine and IV opioids at 15 minutes and 60 minutes, but a tendency of better pain reduction with opioids at 30 minutes. Interesting to note is that the 95% CI of MD at 30 minutes was wide-ranging from 0.06 to 2.13, indicating minimal difference between the two groups to a difference of 2 points. Such inconsistent results in our analysis may be partly explained by the different opioids used in the included studies. In our analysis, IN ketamine was compared with morphine, except in the trial of Mozafari et al[22]. Also, the 30-minute results were largely influenced by the study of Mozafari et al[22] which reported better pain reduction with IV fentanyl as compared to IN ketamine in a population of renal colics. Recently, a double-blind RCT has been demonstrated that the efficacy of fentanyl is better as compared to morphine in renal colics[29]. Comparing our results with pediatric patients, Silva et al[14] in their meta-analysis of four RCTs have reported no statistically significant difference in pain scores between IN ketamine and IN fentanyl. The consistent results in their study can be attributed to uniform reporting of data by all trials and similar comparator group.

Comparing with placebo, we found a non-significant difference but a tendency of better pain reduction with IN ketamine at 15 and 60 minutes. The 95% CI was wide with the lower ends indicating a difference of 2-3 points at these time intervals (15 minutes: -2.34; 60 minutes: -3.04). A statistically significant difference in pain scores was noted only at 30 minutes. We also found that the need for supplemental analgesics was significantly reduced with IN ketamine as compared to placebo. Thus, while our results suggest better pain control with IN ketamine, the evidence is not unequivocal and this may be attributable to the limited number of studies available for analysis. Furthermore, while we analysed limited available data for acute pain management with IN ketamine, literature is also deficient for studies assessing the efficacy of IN ketamine for non-emergent pain, especially in adult patients. But such studies have also reported good efficacy of IN ketamine for pain management. In one such study, Nejati et al[30] have demonstrated that IN ketamine is effective in reducing the pain of digital nerve block as compared to placebo. Similarly, Page et al[31] have indicated that IN ketamine can significantly reduce pain during wound dressing change in cancer patients.

Assessing the safety of analgesic drugs in the ED is as important as their efficacy. None of the included trials reported any serious drug-related adverse events with opioids or ketamine. Common adverse events of ketamine include emergence reaction, dizziness, laryngospasm, and nausea/vomiting[7]. Opioids also have their own set of adverse events which include hypotension, respiratory depression, nausea/vomiting, etc[32]however, controversial for many reasons. One of the primary reasons is the well-known phenomenon of psychological addiction that can occur with the use of these medications. Abuse and diversion of these medications is a growing problem as the availability of these medications increases and this public health issue confounds their clinical utility. Also, the extent of their efficacy in the treatment of pain when utilized on a chronic basis has not been definitively proven. Lastly, the role of opioids in the treatment of chronic pain is also influenced by the fact that these potent analgesics are associated with a significant number of side effects and complications. It is these phenomena that are the focus of this review. Common side effects of opioid administration include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression. Physical dependence and addiction are clinical concerns that may prevent proper prescribing and in turn inadequate pain management. Less common side effects may include delayed gastric emptying, hyperalgesia, immunologic and hormonal dysfunction, muscle rigidity, and myoclonus. The most common side effects of opioid usage are constipation (which has a very high incidence. Of note, emergence reactions can be seen in up to 55% of patients receiving ketamine and are directly related to its NMDA receptor blockade[33]to date, no studies have investigated genetic association of ketamine-induced EP in healthy patients. Objectives The aim of the study was to investigate the feasibility and sample sizes required to explore the relationship between CYP2B6-6 and GRIN2B single-nucleotide polymorphisms and ketamine-induced EP. Methods This cross-sectional, pharmacogenetic candidate, gene pilot study recruited 75 patients having minor elective outpatient surgeries. EP was measured with the Clinician Administered Dissociative State Scale. Genetic association of CYP2B6-6 and GRIN2B (rs1019385 and rs1806191. Dizziness with ketamine has been attributed to similar action on NMDA receptors in the inner ear and vestibular nuclei[34]. In our review, a significantly increased risk of emergent reaction-related symptoms was noted with IN ketamine as compared to opioids as well as placebo. Dizziness was increased with IN ketamine as compared to placebo but not as compared to opioids. Incidence of nausea/vomiting was not found to be different between IN ketamine vs opioids or placebo. Due to limited data from the included trials, we could not compare the exact number of patients experiencing adverse events as well as the incidence of hypotension with opioids. Comparing with previous reviews, Silva et al[14] have reported an increased risk of non-serious adverse events with IN ketamine as compared to IN fentanyl. On the other hand, Balzer et al[26] have found no difference in the incidence of nausea and hypoxic events between IV LDK and IV morphine.

There are some limitations of our review. Foremost, only seven RCTs were available for analysis. Furthermore, due to heterogeneity in the comparator drug and limited availability of data only a few studies could be included in the meta-analysis. Secondly, the study population in the included studies was different. Amongst the three studies comparing IN ketamine vs place-

bo, two included only traumatic pain patients while in the four studies comparing IN ketamine with IV opioids three included only renal colic patients. Thus, the generalization of our results for other pain indications should be carried out with caution. Lastly, due to imprecision of results and risk of bias due to blinding in one trial[21], the certainty of the evidence for the comparison of IN ketamine and opioids were not high. Even for the comparison of pain scores between IN ketamine vs placebo, the certainty of the evidence was deemed to be moderate for comparisons at 15 minutes and 60 minutes.

Conclusions

The results of our first systematic review and meta-analysis indicate that there may be a role of IN ketamine for acute pain management in adults in an emergency setting. There is a tendency for better pain control with IN ketamine as compared to control and the possibility of similar efficacy of IN ketamine as compared to opioids. However, the results are not unequivocal and are limited by the low number of studies in literature and limited pain indications studied. Further RCTs are required to strengthen the evidence.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Todd KH, Ducharme J, Choiniere M, Crandall CS, Fosnocht DE, Homel P, Tanabe P; PEMI Study Group. Pain in the Emergency Department: results of the pain and emergency medicine initiative (PEMI) multicenter study. J Pain 2007; 8: 460-466.
2) Kim HS, Heard KJ, Heard S, Hoppe JA. Opioid prescription fill rates after emergency department discharge. Am J Heal Pharm 2016; 73: 902-907.
3) Smith BC, Vigotsky AD, Apkarian AV, Schnitzer TJ. Temporal Factors associated with opioid prescriptions for patients with pain conditions in an urban emergency department. JAMA Netw Open 2020; 3: e200802.
4) Butler MM, Ancona RM, Beauchamp GA, Yamin CK, Winstanley EL, Hart KW, Ruffner AH, Ryan SW, Ryan RJ, Lindsell CJ, Lyons MS. Emergency department prescription opioids as an initial exposure preceding addiction. Ann Emerg Med 2016; 68: 202-208.
5) Hoppe JA, Kim H, Heard K. Association of emergency department opioid initiation with recurrent opioid use. Ann Emerg Med 2015; 65: 493-499. e4.
6) Ukkonen M, Jämsen E, Zeitlin R, Pauniaho SL. Emergency department visits in older patients: a population-based survey. BMC Emerg Med 2019; 19: 20.
7) Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, Pereira EFR, Albuquerque EX, Thomas CJ, Zarate CA Jr, Gould TD. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. Pharmacol Rev 2018; 70: 621-660.
8) Merelman AH, Perlmutter MC, Strayer RJ. Alternatives to rapid sequence intubation: contemporary airway management with ketamine. West J Emerg Med 2019; 20: 466-471.
9) Sullivan N, Chen C, Siegel R, Ma Y, Pourmand A, Montano N, Meltzer A. Ketamine for emergency sedation of agitated patients: A systematic review and meta-analysis. Am J Emerg Med 2020; 38: 655-661.
10) Poonai N, Canton K, Ali S, Hendrikx S, Shah A, Miller M, Joubert G, Rieder M, Hartling L. Intranasal ketamine for procedural sedation and analgesia in children: a systematic review. PLoS One 2017; 12: e0173253.
11) Karlow N, Schlaepfer CH, Stoll CRT, Doering M, Carpenter CR, Colditz GA, Motov S, Miller J, Schwarz ES. A systematic review and meta-analysis of ketamine as an alternative to opioids for acute pain in the emergency department. Acad Emerg Med 2018; 25: 1086-1097.
12) Karlsen AP, Pedersen DM, Trautner S, Dahl JB, Hansen MS. Safety of intranasal fentanyl in the out-of-hospital setting: a prospective observational study. Ann Emerg Med 2014; 63: 699-703.
13) Whitley GA, Pilbery R. Pre-hospital intranasal analgesia for children suffering pain: a rapid evidence review. Br Paramed J 2019; 4: 24-34.
14) Oliveira JE, Silva L, Lee JY, Bellolio F, Homme JL, Anderson JL. Intranasal ketamine for acute pain management in children: a systematic review and meta-analysis. Am J Emerg Med 2020; 38: 1860-1866.
15) Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Med 2009; 6: e1000097.
16) Higgins J, Thomas J, Chandler J,. Cochrane Handbook for Systematic Reviews of Interventions. Version 6. Cochrane 2019. doi:10.1002/9781119536604
17) Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014; 14: 135.
18) Mohammadshahi A, Abdolrazaghnejad A, Nikzamir H, Safaie A. Intranasal ketamine administration for narcotic dose decrement in patients

suffering from acute limb trauma in emergency department: a double-blind randomized placebo-controlled trial. Adv J Emerg Med 2018; 2: e30.

19) Andolfatto G, Innes K, Dick W, Jenneson S, Willman E, Stenstrom R, Zed PJ, Benoit G. Prehospital Analgesia With Intranasal Ketamine (PAIN-K): a randomized double-blind trial in adults. Ann Emerg Med 2019; 74: 241-250.

20) Bouida W, Bel Haj Ali K, Ben Soltane H, Msolli MA, Boubaker H, Sekma A, Beltaief K, Grissa MH, Methamem M, Boukef R, Belguith A, Nouira S. Effect on opioids requirement of early administration of intranasal ketamine for acute traumatic pain. Clin J Pain 2020; 36: 458-462.

21) Shimonovich S, Gigi R, Shapira A, Sarig-Meth T, Nadav D, Rozenek M, West D, Halpern P. Intranasal ketamine for acute traumatic pain in the Emergency Department: a prospective, randomized clinical trial of efficacy and safety. BMC Emerg Med 2016; 16: 43.

22) Mozafari J, Maleki Verki M, Motamed H, Sabouhi A, Tirandaz F. Comparing intranasal ketamine with intravenous fentanyl in reducing pain in patients with renal colic: a double-blind randomized clinical trial. Am J Emerg Med 2020; 38: 549-553.

23) Pouraghaei M, Moharamzadeh P, Paknezhad SP, Rajabpour ZV, Soleimanpour H. Intranasal ketamine versus intravenous morphine for pain management in patients with renal colic: a double-blind, randomized, controlled trial. World J Urol 2020. doi: 10.1007/s00345-020-03319-4. Epub ahead of print.

24) Farnia MR, Jalali A, Vahidi E, Momeni M, Seyedhosseini J, Saeedi M. Comparison of intranasal ketamine versus IV morphine in reducing pain in patients with renal colic. Am J Emerg Med 2017; 35: 434-437.

25) Martinez V, Derivaux B, Beloeil H; Regional Anaesthesia and the Pain Committee of the French Society of Anaesthesiology and Intensive Care. Ketamine for pain management in France, an observational survey. Anaesth Crit Care Pain Med 2015; 34: 357-361.

26) Balzer N, McLeod SL, Walsh C, Grewal K. Low-dose ketamine for acute pain control in the emergency department: a systematic review and meta-analysis. Acad Emerg Med 2021. doi:10.1111/acem.14159.

27) (ACEP) AC of EP. Policy Statement - Optimizing the Treatment of Acute Pain in the Emergency Department. Available at: https://www.acep.org/globalassets/new-pdfs/policy-statements/optimizing-the-treatment-of- acute-pain-in-the-ed.pdf. Published 2017. Accessed January 10, 2020.

28) Axeen S, Seabury SA, Menchine M. Emergency department contribution to the prescription opioid epidemic. Ann Emerg Med 2018; 71: 659-667.e3.

29) Dezfuli SAT, Yazdani R, Esmaeili M, Kazemi S, Hayati S. Comparison the efficiency of morphine, propofol and fentanyl for controlling acute renal colic in patients admitted to hospital: a randomized double-blind clinical trial. Pakistan J Med Heal Sci 2020;14: 701-704.

30) Nejati A, Jalili M, Abbasi S, Talebi Sarwari F, Bidari A, Ghajarzadeh M, Akhgar A. Intranasal ketamine reduces pain of digital nerve block; a double blind randomized clinical trial. Am J Emerg Med 2019; 37: 1622-1626.

31) Page N, Nirabhawane V. Intranasal ketamine for the management of incidental pain during wound dressing in cancer patients: a pilot study. Indian J Palliat Care 2018; 24: 58-60.

32) Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, Glaser SE, Vallejo R. Opioid complications and side effects. Pain Physician 2008; 11(2 Suppl): S105-120. PMID: 18443635.

33) Aroke EN, Crawford SL, Dungan JR. Pharmacogenetics of ketamine-induced emergence phenomena: a pilot study. Nurs Res 2017; 66: 105-114.

34) Soto E, Flores A, Eróstegui C, Vega R. Evidence for NMDA receptor in the afferent synaptic transmission of the vestibular system. Brain Res 1994; 633: 289-296.