

REVIEW ARTICLE

The Efficacy of Ketamine Administration in Prehospital Pain Management of Trauma Patients; a Systematic Review and Meta-Analysis

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Abstract: **Introduction:** Although previous articles and reviews suggest that ketamine might effectively manage pain in trauma patients, these articles have serious limitations. Accordingly, the current meta-analysis aims to investigate the efficacy of ketamine administration in prehospital pain management of trauma patients. **Method:** In the present meta-analysis, controlled human studies were included. An extensive search was conducted in electronic databases including Medline (via PubMed), Embase, Central, Scopus, Web of Science, and ProQuest, gathering data to the end of 2018. The efficacy and side effects of ketamine administration in pre-hospital pain management were compared with those of opioid analgesics based on standard mean difference (SMD) and odds ratio (OR) calculations with 95% confidence interval (95% CI). **Results:** Data from seven articles were included in the present meta-analysis. Ketamine administration was not more effective than administering morphine or fentanyl in prehospital pain management of trauma patients (SMD = -0.56, 95% CI: -1.38 to 0.26, $p = 0.117$). However, co-administration of ketamine+morphine was considerably more effective than ketamine alone, in alleviating pain in prehospital settings (SMD = -0.62, 95% CI: -1.12 to -0.12, $p = 0.010$). Finally, it was concluded that ketamine alone had less side effects than morphine alone (OR = 0.25, 95% CI: 0.11 to 0.56, $p = 0.001$). However, co-administration of ketamine+morphine increases the risk of side effects to 3.68 times compared to when morphine is prescribed solely (OR=3.68, 95% CI: 1.99 to 6.82, $p<0.001$). **Conclusion:** For the first time, findings of the current meta-analysis demonstrated that ketamine, being administered alone, is an effective and safe medication in prehospital pain management in trauma patients, and can be considered as an acceptable alternative to opioid analgesics.

Keywords: Pain Management; Analgesics, Opioid; Analgesics, Non-Narcotic; Emergency Medical Services; Ketamine

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1. Introduction

Pain management is one of the most challenging issues that emergency medical services encounter. Pain management

becomes prominent in the process of saving a patient's life, since the presence of severe pain harmfully affects the patient's respiration, blood pressure, and heart rate. Severe pain causes physiological and pathological responses in the body, which in the case of inappropriate management, could eventually lead to multi-organ failure and death (1, 2). Administration of opioid analgesics is the routine for acute pain management, but side effects such as respiratory distress limit the use of the mentioned medication (3). Moreover, abuse of

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such medications cannot be neglected. Hence, researchers investigate other possible alternatives for pain management in prehospital settings and even in the emergency departments (4-9).

Ketamine is a non-opioid analgesic, administered in the clinic for decades. This drug not only is a strong analgesic, but also affects the sympathetic nervous system, which in many cases can be beneficial for trauma patients (10). For instance, ketamine increases the average heart rate and blood pressure, which are both favorable for stabilizing the traumatic patients' conditions (11, 12). Furthermore, this medication does not bring about the opioid's dangerous side effects, and practically, does not affect the patient's respiration in any way. Thus, ketamine could be considered as a proper substitute for opioid analgesics.

In recent years, many clinical trials have been conducted, indicating that ketamine can be beneficial in pain management of traumatic patients in prehospital settings. As an example, in 2014, Tran et al. demonstrated that ketamine has analgesic effects equivalent to morphine, while the risk of its respiratory side effects is lower than morphine. Nonetheless, delusion and agitation are other side effects of ketamine (13). In 2018, a systematic review indicated that ketamine has similar efficacy and side effects to other analgesics. However, this study lacks in performing a meta-analysis and defining an appropriate inclusion criteria (14). Another meta-analysis in 2016 illustrated that prescribing low dose ketamine in emergency department is efficient and causes no considerable side effects. Nevertheless, this study did not investigate ketamine's use in prehospital settings and included a small number of articles. Therefore, further investigations are still needed (15). Accordingly, considering the limitations of previous studies, the current meta-analysis is determined to investigate the efficacy of ketamine in prehospital pain management of traumatic patients.

2. Method

2.1. Search Strategy

Two independent reviewers conducted an extensive search in electronic databases including Medline (via PubMed), Embase, Central, Scopus, Web of Science, and ProQuest up to the end of 2018. The search strategy was performed according to keywords, relevant to ketamine in combination with "pain control" and "prehospital". The combination of keywords searched in Medline database is presented in Table 1. In addition to the systematic search, searches were performed in Google search engine and Google Scholar to acquire non-indexed reports. Two strategies were adopted to achieve grey literature. First, all of the authors who had relevant articles were contacted via email to obtain unpublished data, unregistered information and dissertations. Further-

more, a detailed search was carried out in ProQuest database to find relevant studies. In cases of inaccessible online data, authors were contacted. Also, hand-search was conducted on reference lists of relevant studies to find additional articles, which resulted in finding one additional article.

2.2. Inclusion criteria

Clinical trials and cohorts that compared administration of ketamine with analgesics in prehospital pain management, were included. Exclusion criteria consisted of not evaluating prehospital efficacy, absence of placebo control group or morphine treatment group, non-traumatic studies and reviews.

2.3. Quality assessment and Data Extraction

Results of the conducted search were combined and duplicate studies were eliminated using EndNote software. Two independent reviewers screened titles and abstracts of the articles and carefully read potentially eligible studies. Then, the full texts of these articles were assessed and articles that met inclusion criteria were included. Data of the articles were recorded in a check list, designed according to PRISMA statement (16). The recorded data included the name of the first author, published year, patient characteristics recorded in clinical trials, administration route of ketamine, administered dosage, and finally the reported outcomes. In case of disagreement between the two reviewers, a third reviewer studied the findings, and the disagreement was resolved by discussion.

The qualities of studies were evaluated using Cochrane's suggested guidelines (17). Inter rater reliability was assessed, evaluating agreement between the two reviewers. Disagreements were resolved by discussion with a third reviewer.

2.4. Statistical Analysis

All the data are presented as means and standard deviations. Also, the prevalence of side effects was summarized as frequency and were recorded in STATA 14.0. In cases where standard errors were reported, or a 95% confidence interval was displayed, based on the sample size of each study and standard formulas, standard deviations were calculated. For each study, standardized mean difference (SMD) with 95% confidence interval (95% CI) was calculated based on Hedges' g. Then, an effect size was presented for each study. Analyses for evaluating ketamine administration side effects were carried out in two parts. In the beginning, using "metaprop_one" command in statistical program, the prevalence of side effects was calculated. Next, prevalence of side effects was compared between morphine treated groups and ketamine treated groups. Here, odds ratios (OR) were presented with 95% CI. Egger's test was used to evaluate publication bias (18). Heterogeneity between articles was evaluated



using I^2 test, and p values lower than 0.1 or I^2 tests higher than 50% were considered as heterogeneity. In all of the analyses, p values lower than 0.05 were considered significant.

3. Results

3.1. Studies' Characteristics

The search conducted in electronic resources resulted in 893 articles. After eliminating duplicates, 533 non-duplicate records were found. 81 potentially relevant articles were obtained while screening titles and abstracts of the records. Seven of these articles were included in the present meta-analysis (13, 19-24). Four articles were clinical trials, and three articles were historical cohorts. Search algorithm and selection process are demonstrated in Figure 1. These studies embody nine separate experiments. Accordingly, the data of these nine experiments were included in the final analysis. Characteristics of the included studies are represented in Table 2.

In total, 1064 patient data were included in the current meta-analysis. Out of these patients, 470 were treated with ketamine and 507 patients were in the control group or standard treatment group. Control/standard-treatment group patients were treated with fentanyl in two experiments, morphine in six experiments and placebo in one study. In five experiments, ketamine was prescribed alone, and in four studies, ketamine was prescribed along with morphine to evaluate the effects of adding ketamine to morphine in alleviating pain and reducing morphine side effects. All of the studies adopted intravenous administration of ketamine. All of the seven included studies evaluated the efficacy of ketamine in trauma patients' pain management. Nevertheless, ketamine side effects were reported in only five articles.

3.2. Quality assessment of studies and risk of bias

As demonstrated in Table 2 and Figure 2, the risk of bias in matching of patients, proper inclusion and exclusion criteria, and incomplete outcome data was low in all of the articles. However, the risk of bias in allocation concealment, blinding of patients, and blinding of outcome assessment sections was high in 71.4% of the studies. There was no publication bias in efficacy assessment of ketamine administration in pain management (Bias coefficient= -4.44; $p=0.395$). There was also no population bias in evaluation of ketamine administration side effects (Bias coefficient= -1.47; $p=0.831$) (Figure 2).

3.3. Meta-analysis

- The effectiveness of ketamine administration in prehospital pain management of patients

Four studies investigated the efficacy of prescribing ketamine

alone, in prehospital pain management. Analyses in this section revealed that prescribing ketamine alone was not more effective than morphine or fentanyl in prehospital pain management of trauma patients (SMD= -0.56, 95% CI: -1.38 to 0.26, $p=0.117$). Five studies evaluated the efficacy of ketamine+morphine in comparison with morphine alone in prehospital pain management. Administration of ketamine with morphine was more effective than prescribing morphine alone in alleviating trauma patients' pain in prehospital settings (SMD= -0.62, 95% CI: -1.12 to -0.12, $p=0.010$; $I^2=92.6\%$, $p<0.0001$) (Figure 3).

- Prevalence of ketamine side effects in prehospital settings

After administration of ketamine alone, side effects are observed in 2.49% of patients, whereas administration of morphine alone causes side effects in 11.99% of patients. Nevertheless, co-administration of ketamine+morphine increases the rate of side effects to 35.90%. Side effects are less probable when ketamine is administered alone, compared to morphine being used alone (OR=0.25, 95% CI: 0.11 to 0.56, $p=0.001$). Nevertheless, co-administration of morphine+ketamine, increases the odds of side effects 3.68 times compared to when morphine is prescribed alone (OR = 3.68, 95% CI: 1.99 to 6.82, $p<0.001$) (Figure 4). The most prevalent side effect of ketamine reported in studies was Ramsay score higher than three (7.42%). Nonetheless, in groups treated with morphine, nausea and vomiting were the most frequent complications (7.54%). Neuropsychologic side effects in the group treated with ketamine was 6.77%, while the prevalence of these side effects was 0.68 in the morphine-treated group (Table 3). Neuropsychologic side effects include hallucinations, delusions, dizziness, dysphoria, diplopia, and agitation.

4. Discussion

For the first time, the present study meta-analyzed the pre-existing evidence on efficacy of ketamine in prehospital pain management in trauma patients. Findings of this study demonstrated that efficacy of ketamine in prehospital pain management and that of opioid analgesics are similar. However, the side effects of administration of ketamine alone are less than those of opioid analgesics. In addition, the present study depicted that although, to some extent, ketamine+morphine combination is more effective than morphine alone, the side effects of combination treatment are 3.68 times more than morphine treatment alone. Although the included literature in this section believed that ketamine+morphine co-treatment resulted in lower administration dosage of morphine, analyses revealed that not only this low dose morphine does not result in less side effects, but also co-treatment with morphine+ketamine causes an increase in the prevalence of side effects. However, the effect



size of morphine+ketamine co-treatment in alleviating pain is in a weak range (SMD=-0.67). As a result, it seems that administration of ketamine+morphine is not preferable to that of morphine alone.

Compared with the findings of the present study, in 2018 a systematic review (without performing a meta-analysis) demonstrated that ketamine's efficacy is similar to that of other analgesics, and has similar side effects to other medications. Nevertheless, not performing meta-analysis and not having an appropriate inclusion criteria were two major weaknesses of the aforementioned study (14). Findings of the present study were in line with the above-mentioned article, and furthermore, in the present study the efficacy of co-treatment with ketamine and morphine was evaluated. Another meta-analysis in 2017, aiming to evaluate the efficacy of different analgesics on trauma patients' pain management, referred to ketamine as an appropriate medication for use in in-hospital emergency departments. Nonetheless, poor search, not evaluating ketamine's efficacy in prehospital settings and small number of included studies in ketamine section caused their results to be potentially biased (25). Another meta-analysis in 2016 concluded that low dose ketamine is effective in alleviating pain in emergency departments and does not cause any prominent side effects. However, the small number of compiled articles in this study and not evaluating prehospital settings bring forward the need for further investigations (15). Apparently, there are serious limitations in the previous studies and nearly no study was performed on the efficacy of ketamine in prehospital pain management of trauma patients. For the first time, the present meta-analysis quantitatively summarized the available evidence in the aforesaid matter, to overcome the limitations of the previous studies.

The present study conducted an extensive search in electronic resources, contacted authors and searched on web pages to gather the largest number of articles and gray literature. Furthermore, absence of publication bias is one of the strengths of the current study. Still, one of the limitations of the current meta-analysis was presence of considerable heterogeneity. Presence of non-blinded observers in some of the included studies, which may have caused bias in our results, was another limitation of the present study.

5. Conclusion

For the first time, findings of the present meta-analysis demonstrated that ketamine can help manage prehospital pain in trauma patients similar to opioid analgesics and has fewer side effects. However, findings regarding morphine+ketamine co-treatment were different. Analyses showed that although ketamine+morphine administration was somewhat more effective than administration of mor-

phine alone in prehospital pain management of trauma patients, side effects of morphine+ketamine regimen were 3.68 times more than that of morphine alone. As a result, it seems that ketamine+morphine co-administration has no privilege compared to administration of morphine alone. In general, ketamine seems to be an effective and safe medication in prehospital pain management of trauma patients, and can be an alternative to opioid analgesics.

6. Appendix

6.1. Acknowledgements

None

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6.3. Funding Support

None

6.4. Conflict of Interest

None

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Table 1: Medline search query**Search terms**

1- "Emergency Medical Services"[mh] OR "Emergency Health Service"[tiab] OR "Emergency Care"[tiab] OR "Prehospital Medication"[tiab] OR "Prehospital Care"[tiab] OR "Prehospital"[tiab] OR "Emergency Services, Medical"[tiab] OR "Emergency Service, Medical"[tiab] OR "Medical Emergency Service"[tiab] OR "Medical Emergency Services"[tiab] OR "Service, Medical Emergency"[tiab] OR "Services, Medical Emergency"[tiab] OR "Medical Services, Emergency"[tiab] OR "Emergency Medical Service"[tiab] OR "Medical Service, Emergency"[tiab] OR "Service, Emergency Medical"[tiab] OR "Services, Emergency Medical"[tiab] OR "Prehospital Emergency Care"[tiab] OR "Emergency Care, Prehospital"[tiab] OR "Emergicenters"[tiab] OR "Emergicenter"[tiab] OR "Emergency Care"[tiab] OR "Emergency Health Services"[tiab] OR "Emergency Health Service"[tiab] OR "Health Service, Emergency"[tiab] OR "Health Services, Emergency"[tiab] OR "Service, Emergency Health"[tiab] OR "Services, Emergency Health"[tiab]

2- "Wounds and Injuries"[mh] OR "Arm Injuries"[mh] OR "Radius Fractures"[mh] OR "Ulna Fractures"[mh] OR "Forearm Injuries"[mh] OR "Humeral Fractures"[mh] OR "Wrist Injuries"[mh] OR "Injuries "[mh] OR "Multiple Trauma"[mh] OR "Fractures, Multiple"[mh] OR "Fractures, Bone"[mh] OR "Ankle Fractures"[mh] OR "Femoral Fractures"[mh] OR "Hip Fractures"[mh] OR "Fracture Dislocation"[mh] OR "Salter-Harris Fractures"[mh] OR "Fractures, Avulsion"[mh] OR "Fractures, Closed"[mh] OR "Fractures, Comminuted"[mh] OR "Fractures, Compression"[mh] OR "Fractures, Malunited"[mh] OR "Fractures, Multiple"[mh] OR "Fractures, Open"[mh] OR "Fractures, Spontaneous"[mh] OR "Fractures, Stress"[mh] OR "Fractures, Ununited"[mh] OR "Humeral Fractures"[mh] OR "Intra-Articular Fractures"[mh] OR "Osteoporotic Fractures"[mh] OR "Periprosthetic Fractures"[mh] OR "Radius Fractures"[mh] OR "Colles' Fracture"[mh] OR "Rib Fractures"[mh] OR "Shoulder Fractures"[mh] OR "Bankart Lesions"[mh] OR "Skull Fractures"[mh] OR "Jaw Fractures"[mh] OR "Orbital Fractures"[mh] OR "Skull Fracture, Basilar"[mh] OR "Skull Fracture, Depressed"[mh] OR "Zygomatic Fractures"[mh] OR "Spinal Fractures"[mh] OR "Tibial Fractures"[mh] OR "Trauma"[tiab] OR "Traumas"[tiab] OR "Multiple Traumas"[tiab] OR "Traumas, Multiple"[tiab] OR "Polytrauma"[tiab] OR "Polytraumas"[tiab] OR "Trauma, Multiple"[tiab] OR "Injuries, Multiple"[tiab] OR "Injury, Multiple"[tiab] OR "Multiple Injury"[tiab] OR "Multiple Injuries"[tiab] OR "Broken Bones"[tiab] OR "Bone, Broken"[tiab] OR "Bones, Broken"[tiab] OR "Broken Bone"[tiab] OR "Bone Fractures"[tiab] OR "Bone Fracture"[tiab] OR "Fracture, Bone"[tiab] OR "Spiral Fractures"[tiab] OR "Fracture, Spiral"[tiab] OR "Fractures, Spiral"[tiab] OR "Spiral Fracture"[tiab] OR "Torsion Fractures"[tiab] OR "Fracture, Torsion"[tiab] OR "Fractures, Torsion"[tiab] OR "Torsion Fracture"[tiab] OR "Fractures"[tiab] OR "Injuries"[tiab] OR "Arm Injuries"[tiab] OR "Radius Fracture*"[tiab] OR "Ulna Fracture*"[tiab] OR "Forearm Injur*"[tiab] OR "Humeral Fracture*"[tiab] OR "Wrist Injur*"[tiab] OR "Injur*"[tiab] OR "Multiple Trauma"[tiab] OR "Multiple Fracture*"[tiab] OR "Bone Fracture*"[tiab] OR "Ankle Fractures"[tiab] OR "Femoral Fracture*"[tiab] OR "Hip Fracture*"[tiab] OR "Fracture Dislocation"[tiab] OR "Salter-Harris Fracture*"[tiab] OR "Avulsion Fracture*"[tiab] OR "Closed Fracture*"[tiab] OR "Comminuted Fracture*"[tiab] OR "Humeral Fracture*"[tiab] OR "Intra-Articular Fracture*"[tiab] OR "Osteoporotic Fracture*"[tiab] OR "Periprosthetic Fracture*"[tiab] OR "Radius Fracture*"[tiab] OR "Rib Fracture*"[tiab] OR "Shoulder Fracture*"[tiab] OR "Bankart Lesion*"[tiab] OR "Skull Fracture*"[tiab] OR "Jaw Fracture*"[tiab] OR "Orbital Fracture*"[tiab] OR "Spinal Fracture*"[tiab] OR "Tibial Fracture*"[tiab]

3- "Ketamine"[mh] OR "Ketamine"[tiab] OR "2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone"[tiab] OR "CI-581"[tiab] OR "CI 581"[tiab] OR "CI581"[tiab] OR "Ketalar"[tiab] OR "Ketaset"[tiab] OR "Ketanest"[tiab] OR "Calipsol"[tiab] OR "Kalipsol"[tiab] OR "Calypsol"[tiab] OR "Ketamine Hydrochloride"[tiab]

4- #1 AND #2 AND #3



Table 2: Characteristics of included studies

Author; year; country	Study design	Number of patients (ketamine / control)	Sampling method	Age	Number of male	Setting of patients	Control group	Ketamine dosage
Bronsky; 2019; USA	Historical Cohort	79 / 79	Consecutive	>18	61	Adult trauma patients with severe pain	fentanyl/ 2 bolus over the course of 1 to 2 minutes, with an additional dose every 10 minutes as needed	Ketamine 0.3 mg/kg IV every 20 minutes as needed
Galinski; 2007; France	RCT	33 / 32	Consecutive	18-79	48	Adult trauma patients with severe pain	Morphine/ 3 mg every 5 min	Ketamine: 0.2 mg/kg IV during 10 mins and Morphine 3 mg every 5 mins
Jennings; 2016; Australia	RCT	70 / 65	Consecutive	>18	78	Adult trauma patients with moderate to severe pain	Morphine/ initial dose of 5 mg and if needed 1 to 5 mg after 5 min	Ketamine: 10 or 20 mg/kg IV and 10 mg every 3 mins and Morphine initial dose of 5 mg and if needed 1 to 5 mg after 5 min
Johansson; 2009; Sweden	Prospective Cohort	16 / 11	Consecutive	72&15	13	Adult bone fracture patients with severe pain	Morphine/with a dose of 0.2 mg/kg	Ketamine: with a dose of 0.2/kg mg and Morphine with a dose of 0.1 mg/kg
Shackelford; 2015; Afghanistan	Historical cohort	73 / 28	Consecutive	NR	NR	War victim patients	No medication	Ketamine with a mean dose of 50 mg
Tran; 2014; Vietnam	RCT	169 / 139	Consecutive	>18	238	Adult and child trauma patients with moderate to severe pain	Morphine: 10 mg for adult; 5 mg for children single dose	Ketamine: 0.2-0.3 mg/kg IV slowly
Wiel; 2014; France	RCT	30 / 33	NR	>18	44	Isolated orthopaedic injuries secondary to trauma with severe pain	Morphine with a dose of 0.1 mg/kg	Ketamine: a bolus dose of 0.2/kg mg and Morphine with a bolus dose of 0.1 mg/kg and a continuous infusion of ketamine with a dose of 0.2-mg.kg-1.há1.Š1

RCT: Randomized clinical trial; NR: Not reported



Table 3: Quality assessment of included studies

	Bronsky; 2019	Galinski; 2007	Jennings; 2016	Johansson; 2009	Shackelford; 2015	Tran; 2014	Wiel; 2014
Random sequence generation	☺	☺	☺	☺	☺	☺	☺
Allocation concealment	☺	☺	☺	☺	☺	☺	☺
Matching of the patients	☺	☺	☺	☺	☺	☺	☺
Proper inclusion and exclusion criteria	☺	☺	☺	☺	☺	☺	☺
Blinding of the patients	☺	☺	☺	☺	☺	☺	☹
Blinding of outcome assessment	☺	☺	☺	☺	☺	☺	☹
Incomplete outcome data	☺	☺	☺	☺	☺	☺	☺
Selective reporting	☹	☺	☺	☺	☺	☺	☺
Other bias	☺	☺	☹	☺	☺	☺	☺

☺: Low Risk; ☹: High Risk; ☹: Unclear Risk

Table 4: Side effects of ketamine and morphine administration in pain management of trauma patient in prehospital setting.

Complication	Ketamine group		Morphine group	
	Prevalence	95% CI	Prevalence	95% CI
Ramsey score>3	7.42	1.78 to 11.35	1.95	0.00 to 7.58
Nausea and vomiting	3.94	2.03 to 6.33	7.54	4.79 to 10.74
Neuropsychological complication	6.77	4.31 to 9.67	0.68	0.00 to 2.16
Respiratory complication	0.00	0.00 to 0.39	0.32	0.00 to 1.74
Hemodynamic instability	0.05	0.00 to 0.99	0.1	0.00 to 1.23

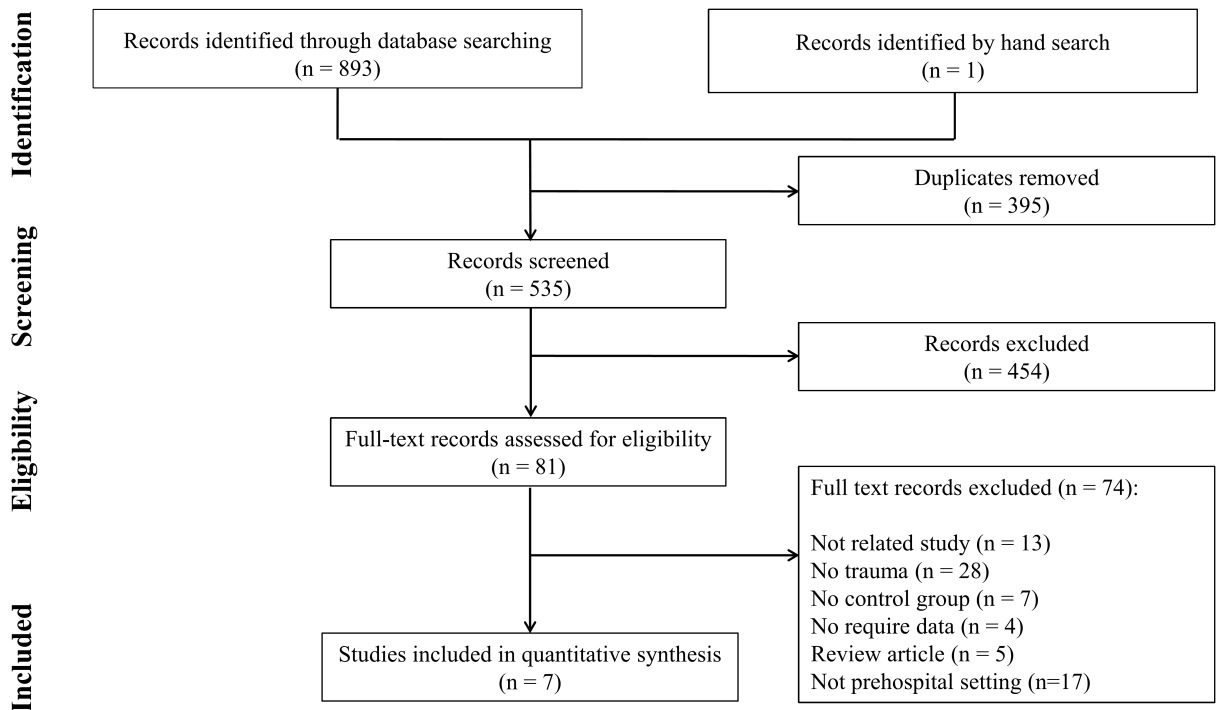
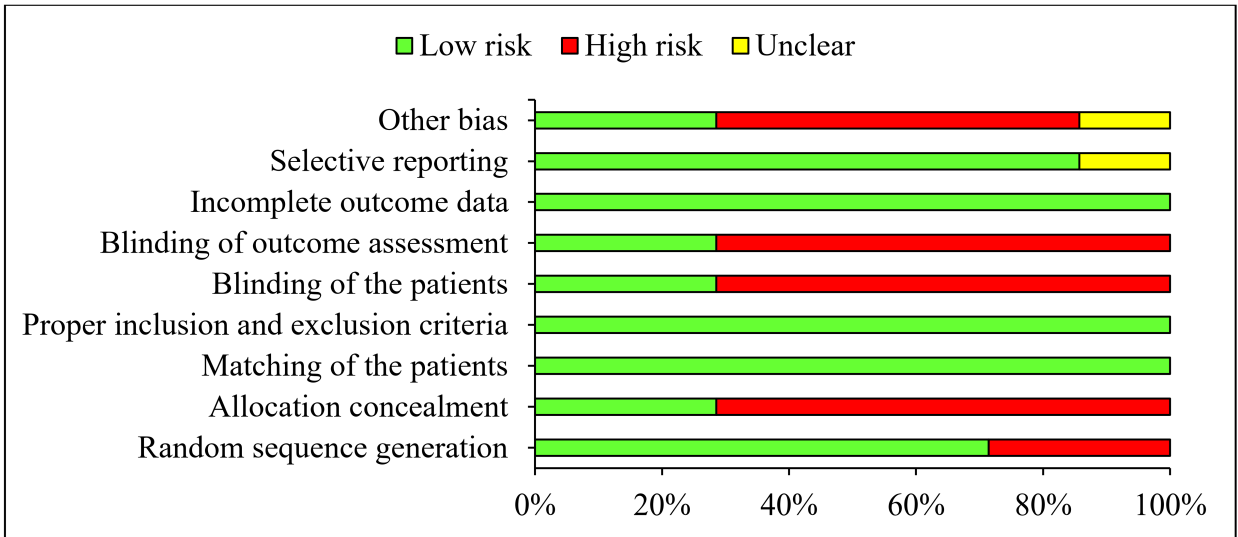


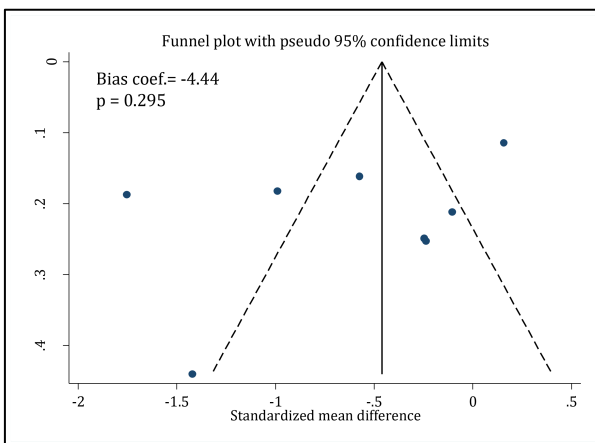
Figure 1: Flowchart of the present meta-analysis.



A



B



C

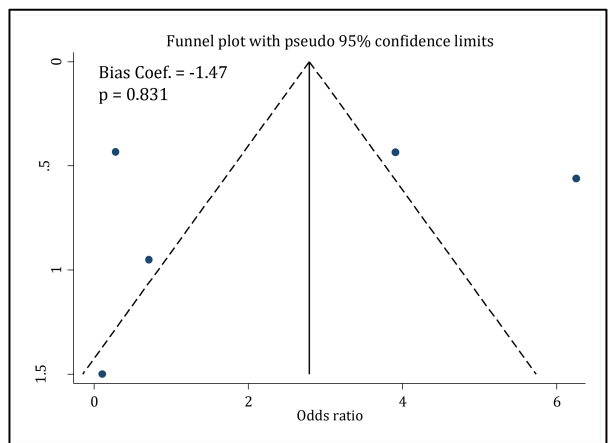


Figure 2: Quality assessment of included articles (A) and evaluation of publication bias regarding efficacy of ketamine in reducing trauma patients' pain (B) and its side effects (C).



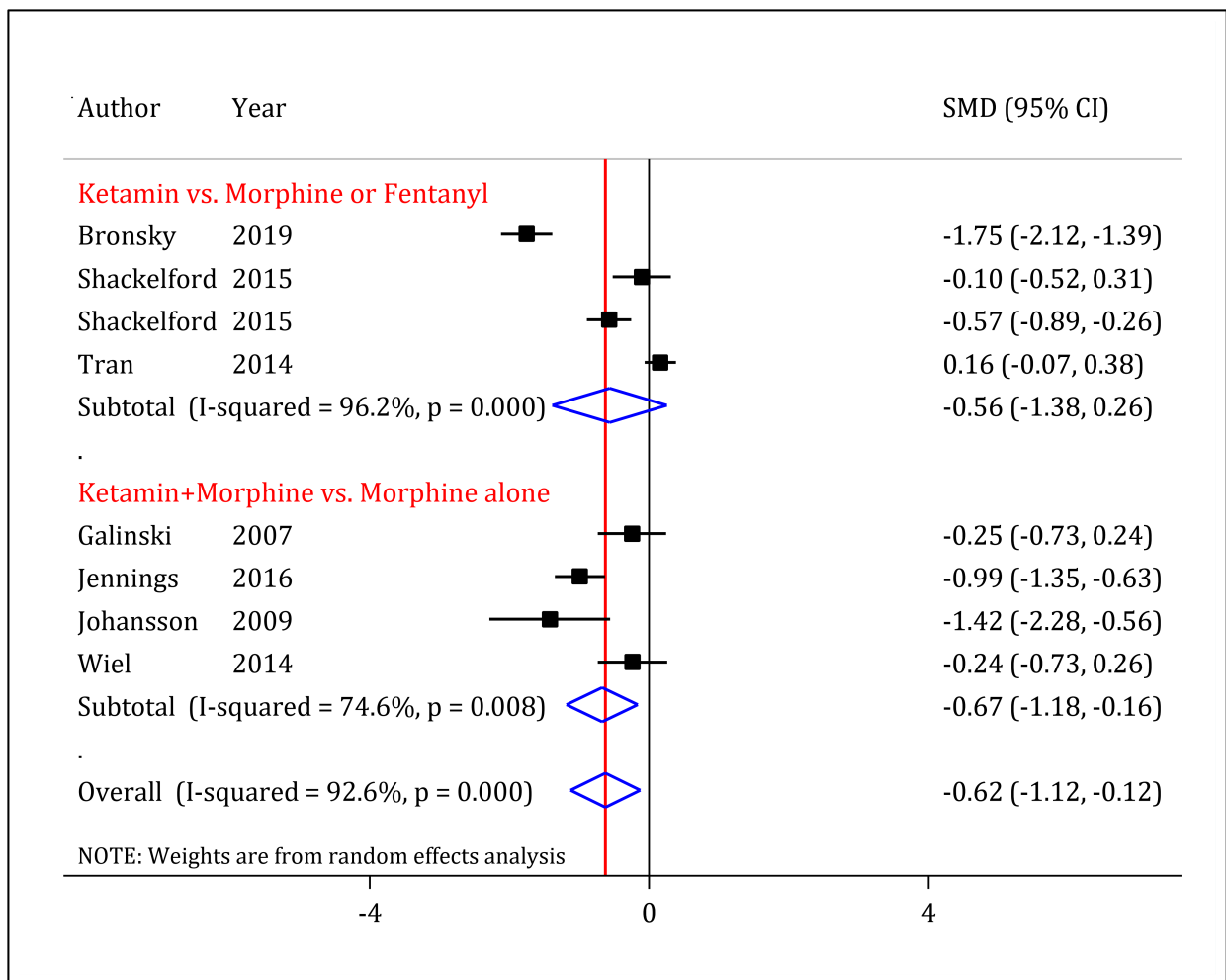
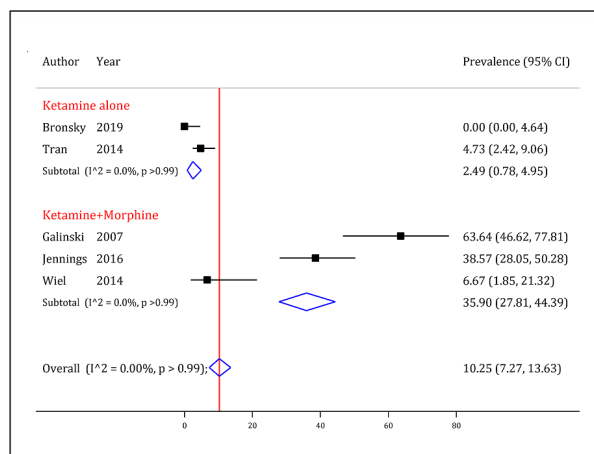


Figure 3: Forest plot of ketamine efficacy in reducing pain severity in trauma patients. SMD: Standardized mean difference; CI: Confidence interval.

A



B

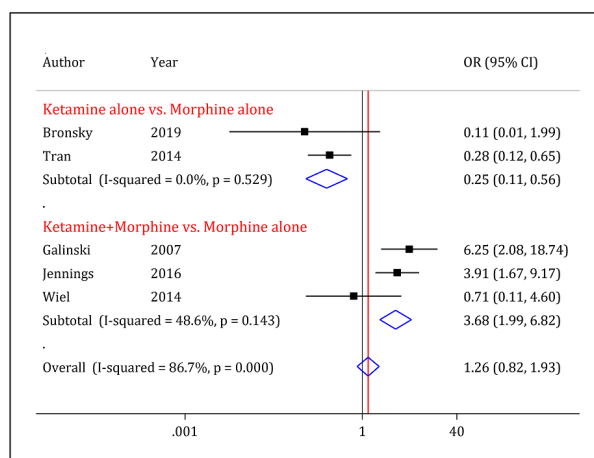


Figure 4: Prevalence of side effects of ketamine alone and ketamine+morphine in trauma patients (A). Odds ratio (OR) for incidence of ketamine side effect (B). CI: Confidence interval.

