Subanaesthetic single-dose ketamine as an adjunct to opioid analgesics for acute pain management in the emergency department: a systematic review and meta-analysis

Stine Fjendbo Galili, Lone Nikolajsen, Nicholas Papadomanolakis-Pakis

ABSTRACT

Objective To evaluate the effectiveness of a subanaesthetic single-dose ketamine (SDK) as an adjunct to opioids for acute pain in emergency department (ED) settings.

Design Systematic review and meta-analysis.

Methods A systematic search was performed in MEDLINE, Embase, Scopus and Web of Science through March 2022. Randomised controlled trials (RCTs) that investigated SDK as an adjunct to opioids in adult patients for any painful condition in ED settings were selected. Two reviewers screened studies, extracted data and assessed study quality. Data were pooled using random-effects models. The primary outcome was mean pain intensity score measured at baseline, >0–15 min, >15–30 min, >30–45 min, 60 min, 90 min and 120 min. Secondary outcomes included need for rescue analgesia, adverse events and patient satisfaction. Results were reported as mean differences (MDs) and risk ratios. Statistical heterogeneity was calculated using the I² statistic.

Results Eight RCTs were included (n=903). Studies were judged to be at moderate to high risk of bias. Mean pain intensity scores were significantly lower 60 min after study drug administration favouring adjuvant SDK (MD −0.76; 95% CI −1.19 to −0.33), compared with opioids alone. There was no evidence of differences in mean pain intensity scores at any other time point. Patients who received adjuvant SDK were less likely to require rescue analgesia (MD −0.06; 95% CI −0.33 to 0.19) and had higher satisfaction scores, compared with opioids alone.

Conclusions Available evidence suggests adjuvant SDK can have an effect on lowering pain intensity scores. Although reduction of pain scores was not clinically significant, the combination of reduced pain intensity and reduced opioid requirements suggest the results could be clinically important and support the potential utility of SDK as an adjunct to opioids to treat acute pain in adult ED patients. However, current evidence is limited and higher quality RCTs are needed.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a comprehensive synthesis and meta-analysis of the effectiveness of a subanaesthetic dose of ketamine as an adjunct analgesic to opioids on pain intensity, rescue analgesia, adverse effects and patient satisfaction for presentations of acute pain in adult emergency department patients.

⇒ This study included all painful conditions offering generalisability but limited available evidence did not allow for assessment of specific conditions.

⇒ The risk of bias across studies is mostly high with considerable heterogeneity, therefore definitive conclusions could not be drawn.

INTRODUCTION

Acute pain is one of the most common presenting complaints in the emergency department (ED) accounting for 70–80% of ED presentations.1–4 As such, acute pain management is an essential component of emergency medicine, yet it remains a challenge to ensure prompt, safe and effective management.5-7 Opioid analgesics remain the mainstay treatment for moderate to severe acute pain in the ED, but have been associated with several adverse side effects including respiratory, cardiovascular, central nervous system, gastrointestinal, endocrine and immune effects.1,8-11 Thus, other pharmaceutical alternatives have been investigated, notably ketamine as a stand-alone agent or adjunct to opioid analgesics.12

Ketamine functions primarily as an antagonist of the N-methyl D-aspartate receptor, thus counteracting signals and impulses that lead to hyperalgesia, central sensitisation and opioid tolerance.13-15 It also reduces the wind-up phenomenon and activates descending inhibitory monoaminergic pain pathways via interaction with opioid receptors. Previous clinical trials have reported...
analgesic and opioid-sparing effects of subanaesthetic ketamine doses in addition to reduced risk of respiratory depression, hypotension and hypoxaemia, compared with opioids alone. The use of subanaesthetic ketamine has been cited as a safe and effective alternative or adjunct to opioids for acute pain in a variety of settings including prehospital, ED and perioperative settings.

Previous systematic reviews and meta-analyses have assessed studies that examined subanaesthetic ketamine as a stand-alone treatment for acute pain in ED and perioperative settings, and for cancer pain. No previous systematic reviews or meta-analyses have examined the effects of subanaesthetic single-dose ketamine (SDK) as an adjunct to opioids for acute pain in the ED. Ketamine has been demonstrated to provide synergistic and/or additive effects, which could result in lower opioid requirements while effectively reducing pain, thus favouring a more acceptable side-effect profile than ketamine or opioids as stand-alone agents. The combined effects of ketamine with opioids could provide additional value for clinicians when considering multimodal analgesia in the ED. Therefore, the primary objective of this systematic review and meta-analysis was to synthesise evidence and evaluate the effect of subanaesthetic SDK as an adjunct to opioids, compared with opioids alone, on pain intensity scores for acute pain in the ED. Secondary objectives included evaluating the effect of the intervention on need for rescue analgesia, adverse events and patient satisfaction.

METHODS
This systematic review and meta-analysis was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy
We searched MEDLINE, Embase, Scopus and Web of Science in August 2021 for peer-reviewed studies published between 2000 and 2021, with an updated search in March 2022. We also searched ClinicalTrials.gov for ongoing studies. The search strategy for each database was informed by randomised controlled trial (RCT) design filters by Haynes et al and developed in collaboration with an experienced librarian. Reference lists from included studies were used to identify additional relevant articles. English studies published in peer-reviewed journals were considered for inclusion. The complete search strategy is provided in data supplement, see online supplemental table 1.

Eligibility criteria
This review included RCTs that examined the use of a single subanaesthetic dose (<1 mg/kg) of ketamine as an adjunct to opioids for any acute pain condition among adult patients aged 18 years and older in ED settings. No restrictions were imposed on the route of administration. Studies that included paediatric populations, investigated the use of ketamine outside ED settings or for uses other than acute pain analgesia (ie, anaesthetic doses ≥1 mg/kg), were excluded. Studies that examined ketamine administered as a stand-alone agent, rather than as an adjunct to opioids, were also excluded. For a complete list of inclusion and exclusion criteria, see online supplemental table 2.

Outcome measures
The primary outcome of interest was reduction in pain intensity assessed clinically by means of any standardised pain screening tool following administration of an opioid analgesic with adjuvant SDK, compared with opioids alone. Secondary outcomes included need for rescue analgesia, adverse events and patient satisfaction with pain control.

Screening and data extraction
All studies identified during the literature search underwent a full independent dual review process (SFG and NP-P). Disagreements were discussed and resolved with a third reviewer (LN). The screening process was facilitated by the use of Covidence (https://www.covidence.org) and the selection process was documented using the PRISMA flow diagram. Data extraction was completed by two independent reviewers (SFG and NP-P) using a predefined standardised data extraction form in Covidence. Study authors were contacted in case of missing data. Items for data extraction were informed by the PRISMA checklist and the Cochrane Handbook for Systematic Reviews of Interventions and included participants, study design, interventions, controls, setting, methods, outcomes and results.

Risk of bias assessment
Risk of bias (ROB) for the primary outcome was independently assessed by two reviewers (SFG and NP-P) with respect to the effect of assignment to the intervention at baseline using Risk of Bias 2 (RoB 2): a revised tool for assessing ROB in randomised trials. RoB 2 is organised into five domains: randomisation process, effect of assignment to intervention, missing outcome data, measurement of outcome and the reported result. The ROB in each domain was judged as low, high or some concerns. Disagreements were discussed and resolved with a third reviewer (LN).

Synthesis and data analysis
All RCTs included in the review were narratively described with key findings tabulated. We compared effect estimates across studies taking into consideration the quality of the study and accuracy of findings. The timing of pain score measurements were categorised based on a previous study. Clinical relevance and availability of data (preadministration, >0–15 min, >15–30 min, >30–45 min, 60 min, 90 min and 120 min). Need for rescue analgesia was categorised as patients who received at least one rescue dose during the study period, patients who received a rescue dose 10–20 min after study drug administration

and patients who received a rescue dose 30–40 min after study drug administration. Adverse events were categorised as nausea or vomiting, dysphoria or agitation and hypoxia and hypotension.

Pooled analyses of continuous outcomes (pain intensity and patient satisfaction scores) were performed using restricted maximum-likelihood random-effects models and reported as mean differences (MDs) with 95% CIs. Dichotomous outcomes (need for rescue analgesia and adverse events) were compared using Mantel-Haenszel random-effects models and reported as risk ratios (RRs) with 95% CIs. Statistical significance was set at two-sided p<0.05. In cases of missing data or if medians rather than means were reported, SDs were estimated according to formulas described by Cochrane and means imputed based on the sample size, median and IQR as described by Wan et al. The proportion of total variability due to between study variance was estimated using the $I^2$ statistic with 95% CIs. A post hoc sensitivity analysis was performed on the primary outcome by omitting outlying studies found to contain significant clinical diversity in study protocols. All analyses were conducted using meta and metafor packages in R software, V.4.1.2 (R Foundation for statistical computing).

**Patient and public involvement**
No patient was involved.

**RESULTS**

**Search results**
The primary search identified 379 records (figure 1). After removal of duplicates, 239 titles and abstracts were screened, 19 articles were reviewed in full text and

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**Figure 1** PRISMA flow diagram (adapted from Moher et al). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
11 articles were subsequently excluded. A total of eight studies met eligibility criteria and were included for narrative analysis; seven of the eight studies provided data for at least one outcome and were included in the meta-analysis.

**Study and patient characteristics**

All included studies were published between 2014 and 2020 (table 1). Five studies were conducted in Iran39–43 and three were from the USA.17 44–45 A total of 903 patients were randomised to treatment arms; of which 897 patients were included in formal analyses (69.1% were male; 485 were assigned to intervention and 412 to control). Sample sizes ranged from 6044–45 to 20042 patients. Five studies reported the mean age of patients ranging from 31.6 years 43 to 42.517 years. Three studies examined patients with an acute pain score ≥3,45 ≥544 or ≥617 out of 10 on an 11-point Numerical Rating Scale (NRS), two studies examined patients with limb trauma, 40 45 two studies examined patients with renal colic and NRS ≥644 and one study examined patients with long bone fractures and NRS ≥7.41

All studies administered a single predefined dose of adjuvant S-ketamine at the start of the study, however doses and routes of administration varied between studies; adjuvant SDK was administered intravenously in six studies,17 39 40 42 44 45 intranasally in one study43 and by inhalation in one study.41 Adjuvant SDK doses administered intravenously varied between 0.1 mg/kg17 and 0.3 mg/kg. 40 44–45 Adjuvant SDK doses administered by intranasal (IN) and inhalation routes were 1.0 mg/kg 41 and 1.5 mg/kg, respectively.41 Based on bioavailability of IN (25%–50%) 46 and nebulised (inhaled) (20%–40%) 47 48 ketamine, the systemic absorption for adjuvant SDK10–20 mg/kg43 and 1.5 mg/kg nebulised ketamine would approximate 0.25–0.5 mg/kg and 0.3–0.6 mg/kg intravenous (IV) ketamine, respectively. Doses and routes of morphine administration also varied; six studies administered 0.1 mg/kg,39–42 44 45 one study administered 0.05 mg/kg 40 and one study administered provider-determined morphine or equivalent doses.17 In seven studies, repeat doses of morphine or equivalent were administered intermittently until a specific pain threshold was reached;17 39 40 42 45 one study administered a single dose of morphine and excluded patients that required rescue analgesia.41 Detailed information on included studies is provided in online supplemental appendix 1.

**Risk of bias**

Six17 39–41 43 45 of the included studies were judged to be at high ROB and two24 44 were at moderate ROB, with respect to the primary outcome (see online supplemental figures 1 and 2). Bias was introduced by various means; however certain limitations were shared by several studies, notably bias arising from the randomisation process, missing outcome data and selection of the reported result. Specifically, randomisation processes were either not adequately reported or led to important baseline differences between intervention groups, missing outcome data were not adequately reported, and analysis plans were not prespecified or lacked sufficient detail.

**Primary outcome**

**Pain intensity**

Seven of eight studies contained sufficient data to be included in the meta-analysis for the primary outcome.17 39 41–45 We found a significant difference in mean pain intensity scores favouring adjuvant SDK 60 min after study drug administration (MD −0.76; 95% CI −1.19 to −0.33) (figure 2). There was no evidence of differences in mean pain intensity observed at other time points. However, there was a small significant difference in mean pain intensity scores at baseline favouring the intervention group (MD −0.19; 95% CI −0.34 to −0.04).

A sensitivity analysis was conducted omitting Bowers et al17 and Azizkhani et al41 since study protocols differed significantly from the remaining studies. After omission, significant differences in mean pain intensity scores favouring adjuvant SDK were observed >15–30 min (MD −1.09; 95% CI −1.78 to −0.39) and 60 min (MD −0.78; 95% CI −1.32 to −0.24), after study drug administration (figure 3 and table 2). No significant difference in mean pain intensity scores was observed at baseline.

**Secondary outcomes**

**Need for rescue analgesia**

Four studies reported data on the need for rescue analgesia.17 39 43–44 There were significant risk reductions in the need for rescue analgesia among patients who received adjuvant SDK 10–20 min (RR 0.45; 95% CI 0.27 to 0.74) and 30–40 min (RR 0.40; 95% CI 0.21 to 0.75) after study drug administration, compared with opioids alone (figure 4).

**Adverse events**

Six studies reported incidence of nausea and/or vomiting.17 39 41–45 three studies reported dysphoria,39 40 44 two studies reported hypoxia39 44 and two studies reported hypotension39 44 after study drug administration. Pooled estimates suggest no significant difference in risk of nausea or vomiting between intervention groups (RR 0.83; 95% CI 0.46 to 1.53) (figure 5). An increasing trend between dose of adjuvant SDK and risk of dysphoria was demonstrated when SDK was administered at 0.15 mg/kg (RR 4.34; 95% CI 0.95 to 19.79) and 0.3 mg/kg (RR 12.01; 95% CI 2.32 to 62.06), compared with opioids alone. Finally, risk of hypoxia (RR 0.23; 95% CI 0.04 to 1.35) and hypotension (RR 0.21; 95% CI 0.02 to 1.81), although not significant, may be lower among patients who received adjuvant SDK.

**Patient satisfaction with pain control**

Two studies reported patient satisfaction on a 5-point Likert Scale rated as very low, low, fair, good or excellent.40 41 The pooled estimate suggested a significant difference in mean patient satisfaction with pain control
<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Number randomised</th>
<th>Clinical condition(s) and pain scale</th>
<th>Intervention: SDK+morphine equivalent dose</th>
<th>Control: morphine equivalent dose</th>
<th>Administration route</th>
<th>Rescue morphine equivalent dose (IV)</th>
<th>Trial duration (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbasi et al 2020, Iran</td>
<td>187</td>
<td>Limb trauma (fracture, soft tissue damage) VAS</td>
<td>Arm 1: 0.15 mg/kg, Arm 2: 0.3 mg/kg + 0.1 mg/kg</td>
<td>0.1 mg/kg</td>
<td>IV</td>
<td>0.05 mg/kg</td>
<td>180</td>
</tr>
<tr>
<td>Abbasi et al 2018, Iran</td>
<td>106</td>
<td>Renal colic VAS</td>
<td>0.15 mg/kg + 0.1 mg/kg</td>
<td>0.1 mg/kg</td>
<td>IV</td>
<td>0.1 mg/kg</td>
<td>120</td>
</tr>
<tr>
<td>Azizkhani et al 2018, Iran</td>
<td>88</td>
<td>Traumatic long-bone fractures + NRS &gt;7/10</td>
<td>1.5 mg/kg + 0.1 mg/kg</td>
<td>0.1 mg/kg</td>
<td>Intervention: Inhalation, Control: IV</td>
<td>NR</td>
<td>30</td>
</tr>
<tr>
<td>Beaudoin et al 2014, USA</td>
<td>69</td>
<td>Acute pain NRS ≥5/10 with duration &gt;7 days requiring IV opioids</td>
<td>Arm 1: 0.15 mg/kg, Arm 2: 0.3 mg/kg + 0.1 mg/kg</td>
<td>0.1 mg/kg</td>
<td>IV</td>
<td>0.05–0.1 mg/kg</td>
<td>120</td>
</tr>
<tr>
<td>Bowers et al 2017, USA</td>
<td>116</td>
<td>Acute pain NRS ≥6/10</td>
<td>0.1 mg/kg + Provider determined morphine equivalent dose</td>
<td>Provider determined</td>
<td>IV</td>
<td>0.05 mg/kg</td>
<td>120</td>
</tr>
<tr>
<td>Hosseininejad et al 2019, Iran</td>
<td>200</td>
<td>Renal colic + VAS ≥6/10</td>
<td>0.2 mg/kg + 0.1 mg/kg</td>
<td>0.1 mg/kg</td>
<td>IV</td>
<td>0.05 mg/kg</td>
<td>40</td>
</tr>
<tr>
<td>Mohammadshahi et al 2018, Iran</td>
<td>80</td>
<td>Traumatic injury limb pain NRS ≥7/10</td>
<td>1.0 mg/kg + 0.05 mg/kg</td>
<td>0.05 mg/kg</td>
<td>IN</td>
<td>0.5 mg/kg</td>
<td>180</td>
</tr>
<tr>
<td>Sin et al 2017, USA</td>
<td>60</td>
<td>Acute pain NRS ≥3/10</td>
<td>0.3 mg/kg + 0.1 mg/kg</td>
<td>0.1 mg/kg</td>
<td>IV</td>
<td>0.1 mg/kg</td>
<td>120</td>
</tr>
</tbody>
</table>

IN, intranasal; IV, intravenous; NR, not reported; NRS, Numerical Rating Scale; SDK, single-dose ketamine; VAS, Visual Analog Scale.
### Figure 2

Primary analysis forest plot of pooled mean difference estimates for pain intensity scores assessed at different time points after study drug administration. MD, mean difference; SDK, single-dose ketamine.
favouring adjuvant SDK (MD 0.56; 95% CI 0.35 to 0.76) (see online supplemental figure 3).

Heterogeneity
The small number of included studies resulted in imprecise heterogeneity estimates as evidenced by the wide CIs for $I^2$. However, there are noteworthy differences in study protocols that may have contributed to between-study heterogeneity providing justification for the sensitivity analysis. First, in Bowers et al., a provider determined dose of morphine or equivalent was administered up to 30 min prior to SDK administration, whereas all other included studies administered a standardised dose of

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjuvant SDK</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-administration</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Sin 2017</td>
<td>8.67</td>
<td>2.25</td>
</tr>
<tr>
<td>Mohammadhshahi 2018</td>
<td>8.50</td>
<td>1.16</td>
</tr>
<tr>
<td>Abbasi 2018</td>
<td>7.94</td>
<td>0.90</td>
</tr>
<tr>
<td>Hosseininejad 2019</td>
<td>7.98</td>
<td>1.01</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>223</td>
<td>-0.14 [-0.38; 0.10]</td>
</tr>
</tbody>
</table>

Heterogeneity: $T^2 = 0.014 [0.000; 1.409]; Chi^2 = 4, df = 3 (P = 0.26); I^2 = 25% [0%; 71%]
Test for overall effect: Z = -1.13 (P = 0.26)

>0-15 minutes
| Study                  | Mean | SD  | Total | Mean | SD  | Total | MD [95% CI] |
| Sin 2017               | 3.39 | 4.73 | 30    | 6.33 | 3.89 | 30    | -2.40 [-4.59; -0.21] |
| Mohammadhshahi 2018    | -1.55 | 1.93 | 40    | -1.38 | 1.35 | 40    | -0.17 [-0.90; 0.56] |
| Abbasi 2018            | 4.58 | 3.02 | 53    | 5.98 | 3.02 | 53    | -1.40 [-2.55; -0.25] |
| Total (95% CI)         | 123  | -1.04 [-2.24; 0.16] |

Heterogeneity: $T^2 = 0.698 [0.000; 48.626]; Chi^2 = 5.74, df = 2 (P = 0.06); I^2 = 65% [0%; 90%]
Test for overall effect: Z = -1.70 (P = 0.09)

>15-30 minutes
| Study                  | Mean | SD  | Total | Mean | SD  | Total | MD [95% CI] |
| Beaudoin 2014          | -4.54 | 2.79 | 20    | -1.82 | 1.99 | 20    | -2.72 [-4.22; -1.22] |
| Sin 2017               | 3.43 | 3.98 | 30    | 5.33 | 3.89 | 30    | -1.90 [-3.89; 0.09] |
| Mohammadhshahi 2018    | -3.43 | 2.21 | 40    | -2.85 | 1.78 | 40    | -0.58 [-1.46; 0.30] |
| Abbasi 2018            | 3.68 | 1.90 | 53    | 4.80 | 1.90 | 53    | -1.12 [-1.84; -0.40] |
| Hosseininejad 2019     | 4.75 | 0.93 | 100   | 5.26 | 1.13 | 100   | -0.51 [-0.80; -0.22] |
| Total (95% CI)         | 243  | -1.09 [-1.78; -0.39] |

Heterogeneity: $T^2 = 0.376 [0.003; 6.858]; Chi^2 = 11.34, df = 4 (P = 0.02); I^2 = 65% [7%; 87%]
Test for overall effect: Z = -3.07 (P < 0.01)

>30-45 minutes
| Study                  | Mean | SD  | Total | Mean | SD  | Total | MD [95% CI] |
| Sin 2017               | 3.33 | 5.25 | 29    | 5.50 | 4.28 | 29    | -2.17 [-4.64; 0.30] |
| Hosseininejad 2019     | 2.67 | 0.99 | 100   | 3.13 | 1.06 | 100   | -0.46 [-0.74; -0.18] |
| Total (95% CI)         | 129  | -0.86 [-2.28; 0.56] |

Heterogeneity: $T^2 = 0.660; Chi^2 = 1.82, df = 1 (P = 0.18); I^2 = 45%
Test for overall effect: Z = -1.19 (P = 0.24)

60 minutes
| Study                  | Mean | SD  | Total | Mean | SD  | Total | MD [95% CI] |
| Beaudoin 2014          | -4.18 | 2.79 | 20    | -2.18 | 1.99 | 20    | -2.00 [-3.50; -0.50] |
| Sin 2017               | 3.93 | 5.86 | 28    | 5.00 | 4.67 | 27    | -1.07 [-3.87; 1.73] |
| Mohammadhshahi 2018    | -5.23 | 1.90 | 40    | -4.45 | 1.99 | 40    | -0.78 [-1.63; 0.07] |
| Abbasi 2018            | 2.62 | 1.63 | 53    | 3.10 | 1.63 | 53    | -0.48 [-1.10; 0.14] |
| Total (95% CI)         | 141  | -0.78 [-1.32; -0.24] |

Heterogeneity: $T^2 = 0.043 [0.000; 5.588]; Chi^2 = 3.44, df = 3 (P = 0.33); I^2 = 13% [0%; 87%]
Test for overall effect: Z = -2.84 (P = 0.01)

90 minutes
| Study                  | Mean | SD  | Total | Mean | SD  | Total | MD [95% CI] |
| Sin 2017               | 5.00 | 3.92 | 25    | 5.00 | 3.57 | 25    | 0.00 [-2.19; 2.19] |
| Abbasi 2018            | 1.62 | 1.19 | 53    | 1.56 | 1.19 | 53    | 0.06 [-0.39; 0.51] |
| Total (95% CI)         | 78   | 0.06 [-0.39; 0.50] |

Heterogeneity: $T^2 = 0, Chi^2 = 0, df = 1 (P = 0.96); I^2 = 0%
Test for overall effect: Z = 0.25 (P = 0.80)

120 minutes
| Study                  | Mean | SD  | Total | Mean | SD  | Total | MD [95% CI] |
| Sin 2017               | 4.17 | 5.16 | 21    | 4.77 | 2.18 | 17    | -0.60 [-3.04; 1.84] |
| Beaudoin 2014          | -4.36 | 3.99 | 20    | -1.78 | 2.07 | 20    | -2.58 [-4.55; -0.61] |
| Mohammadhshahi 2018    | -6.13 | 1.91 | 40    | -6.25 | 1.71 | 40    | 0.12 [-0.67; 0.91] |
| Abbasi 2018            | 0.90 | 0.70 | 53    | 0.82 | 0.70 | 53    | 0.08 [-0.19; 0.36] |
| Total (95% CI)         | 134  | -0.42 [-1.45; 0.60] |

Heterogeneity: $T^2 = 0.681 [0.000; 21.584]; Chi^2 = 7.18, df = 3 (P = 0.07); I^2 = 56% [0%; 86%]
Test for overall effect: Z = -0.80 (P = 0.42)

Figure 3 Sensitivity analysis forest plot of pooled mean difference estimates for pain intensity scores assessed at different time points after study drug administration. MD, mean difference; SDK, single-dose ketamine.
morphine with adjuvant SDK. Second, Azizkhani et al.\textsuperscript{41} compared nebulised SDK and morphine by inhalation route to IV morphine without placebo. The use of intravenous morphine may have contributed to significant differences in mean pain scores favouring the comparator over adjuvant SDK. In addition, heterogeneity may have been attributable to differences in patient populations (age, sex, clinical condition) and varying doses of SDK and opioid analgesia administered between studies.

Publication bias
Since the number of included studies was small, it was not possible to statistically investigate publication bias. However, forest plots for the primary outcome demonstrated small-study effects where small RCTs were more likely to report larger treatment effects compared with larger RCTs.\textsuperscript{49,50} This could indicate that small RCTs with favourable results were more likely to be published than those with unfavourable results.

**Table 2** Comparison of pooled estimates and heterogeneity between primary and sensitivity analyses

<table>
<thead>
<tr>
<th>Time point</th>
<th>Primary analysis overall effect, (95% CI); N trials; $I^2$ (95% CI)</th>
<th>Sensitivity analysis overall effect, (95% CI); N trials; $I^2$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preadministration</td>
<td>MD=−0.19 (−0.34 to −0.04); 6; 24% (0% to 68%)</td>
<td>MD=−0.14 (−0.38 to 0.10); 4; 25% (0% to 71%)</td>
</tr>
<tr>
<td>&gt;0–15 min</td>
<td>MD=−0.30 (−2.22 to 1.62); 4; 94% (87% to 97%)</td>
<td>MD=−1.04 (−2.24 to 0.18); 3; 65% (0% to 90%)</td>
</tr>
<tr>
<td>&gt;15–30 min</td>
<td>MD=−0.44 (−1.77 to 0.89); 6; 94% (90% to 96%)</td>
<td>MD=−1.09 (−1.78 to −0.39); 5; 65% (7% to 87%)*</td>
</tr>
<tr>
<td>&gt;30–45 min</td>
<td>MD=−0.86 (−2.28 to 0.56); 2; 45%</td>
<td>MD=−0.86 (−2.28 to 0.56); 2; 45%</td>
</tr>
<tr>
<td>60 min</td>
<td>MD=−0.76 (−1.19 to −0.33); 5; 0% (0% to 79%)*</td>
<td>MD=−0.78 (−1.32 to −0.24); 4; 13% (0% to 87%)*</td>
</tr>
<tr>
<td>90 min</td>
<td>MD=−0.57 (−1.80 to 0.67); 3; 76% (19% to 93%)</td>
<td>MD=0.06 (−0.39 to 0.50); 2; 0%</td>
</tr>
<tr>
<td>120 min</td>
<td>MD=−0.62 (−1.56 to 0.33); 5; 64% (5 to 86%)</td>
<td>MD=−0.42 (−1.45 to 0.60); 4; 58% (0% to 86%)</td>
</tr>
</tbody>
</table>

*p<0.01 for overall effect.
MD, mean difference.

**DISCUSSION**
This is the first systematic review and meta-analysis that examined the effect of SDK as an adjunct to opioids on pain intensity, need for rescue analgesia, adverse events and patient satisfaction among patients with acute pain in the ED. Findings suggest adjuvant SDK was associated with a small reduction in pain intensity scores and lower opioid requirements without increased risk of serious adverse side effects, compared with opioids alone. The combination of reduced pain intensity and lower opioid requirements suggest the results could be clinically relevant for acute pain treatment in patients who require opioid analgesia in the ED.\textsuperscript{51}

Findings from the primary analysis suggest adjuvant SDK was associated with a small reduction in pain scores 60 min after study drug administration and the sensitivity analysis suggests an additional association favouring adjuvant SDK >15–30 min after study drug administration.

**Figure 4** Forest plot of pooled risk estimates for rescue analgesia after study drug administration. SDK, single-dose ketamine.
The sensitivity analysis demonstrated a possible clinically important reduction in pain intensity scores (>1 point difference on NRS) 51 60 min after study drug administration in favour of adjuvant SDK. Previous meta-analyses that examined SDK as a stand-alone agent found no differences in pain intensity scores among patients with acute pain in ED settings. For example, a pooled analysis of three RCTs (261 patients) demonstrated SDK administered as a single agent was non-inferior to IV morphine in terms of mean change in NRS. 20 In a pooled subgroup analyses of RCTs that examined ketamine versus placebo (n=2; 105 patients), ketamine versus morphine (n=3; 270 patients) and ketamine versus fentanyl (n=1; 63 patients), the effects of ketamine on pain reduction were similar to opioid analgesics. 23 Finally, a pooled analysis of eight RCTs (1191 patients) found no significant difference in mean pain scores between SDK as a single agent and morphine within the first 60 min after study drug administration. 24 Similar findings have also been documented in prehospital and perioperative settings. 13 25 26 52 The results of our analysis extend the benefit of SDK as a stand-alone agent and demonstrate SDK could be a useful adjuvant analgesic for acute pain.

Five studies included in this review reported either a significantly lower number of requests for, or lower volumes of, opioid rescue analgesia among patients who received adjuvant SDK, compared with opioids alone. 17 39 40 42 43 One included study reported the overall mean opioid dose administered during a study period of 120 min and found patients who received SDK with morphine had lower overall analgesic requirements (9.95±5.83 milligrams of morphine equivalents) than patients who received morphine with placebo (12.81±6.81 milligrams of morphine equivalents). 17 A second included study reported the overall median opioid dose administered during a 120 min study period with similar but non-significant findings, likely due to small treatment group sizes. 44 These findings, in addition to our pooled analyses, provide evidence in support of adjuvant SDK as an opioid-sparing agent when added to opioids to treat moderate to severe acute pain.

Figure 5 Forest plot of pooled risk estimates for reported adverse events after study drug administration. SDK, single-dose ketamine.
Consistent with previous findings in studies examining SDK as a stand-alone analgesic for acute pain treatment, the incidence of common side effects in our study were not statistically significant between treatment groups. However, we did observe a significantly higher risk of dysphoria when adjuvant SDK was administered at 0.3 mg/kg. In a previous meta-analysis, 0.2–0.3 mg/kg of stand-alone ketamine was associated with a higher risk of neurological and psychological events among ED patients with acute pain when compared with opioids. However, opioids were associated with a higher risk of major cardiopulmonary events. Our results demonstrated SDK may be administered as an adjunct to opioids for acute pain without increased risk of serious adverse events.

Finally, pooled estimates demonstrated significantly higher patient satisfaction with pain management among patients who received adjuvant SDK, compared with opioids alone. One additional study included in this review reported patient satisfaction on a 10-point Likert Scale and found patients who received adjuvant SDK had a significantly higher mean satisfaction score (8.57±2.1), than patients who received placebo (6.05±2.6) (p=0.01). Possible contributing factors for higher satisfaction associated with adjuvant SDK include pain intensity reduction, opioid-sparing effects and less severe opioid-related side effects.

Although ketamine is not superior to opioids as a stand-alone treatment in reduction of pain scores, it may provide additive and/or synergistic effects in multimodal treatment with opioids. Ketamine has been demonstrated to delay desensitisation of opioid receptors resulting in prolonged opioid effect which could in part explain its ability to reduce rescue opioid requirements. When administered as an adjunct to opioids, ketamine could provide value in lowering doses for each medication while providing effective analgesia, thus favouring a more acceptable side-effect profile than ketamine or opioids as stand-alone agents.

It is worth noting the variation in pharmacokinetic characteristics between the IV, IN and inhalation routes of ketamine administration included in this review. The bioavailability of IV ketamine is almost 100%, compared with 25%–50% and 20%–40% for the IN and inhalation routes, respectively. Onset of effect for IV ketamine occurs within 30s and 5–10 min for IN administration. The onset of effect for nebulised (inhaled) ketamine has not been reported. The time to maximum concentration (T_max) for ketamine also varies between routes of administration. Intravenous ketamine has a T_max of 1.17 min compared with IN (5–22 min) and inhalation (15–22 min). The half-life of IV ketamine is 2–3 hours in adults. There is no evidence that suggests the half-life of ketamine is affected by the route of administration.

The pharmacokinetic properties of IV and IN ketamine are well understood, however there is currently little evidence surrounding the use of nebulised (inhaled) ketamine for acute pain. Previous case studies have reported the use of nebulised ketamine doses for acute pain in the ED between 0.75 mg/kg to 1.5 mg/kg, approximately equivalent to 0.15–0.6 mg/kg IV ketamine. The availability of various administration forms provides the opportunity for individualised multimodal pain treatment. However, consideration should be given to the varying pharmacokinetic properties of different administration routes.

Currently, no single standard of care exists to treat acute pain in ED settings, however guidelines on the use of ketamine for acute pain management are available. In ED patients who require opioid analgesia to treat moderate to severe acute pain, adjuvant SDK could have a significant role in a multimodal approach to pain management due to ketamine’s unique mechanism of action and side-effect profile. Our study findings provide evidence in support of guidelines that suggest SDK as an adjunct to opioids for acute pain management can reduce pain scores and overall opioid requirements without increasing adverse side effects. Multimodal patient-centred pain treatment can contribute to minimising risk of undesirable opioid-related side effects and subsequent opioid-related outcomes.

**Limitations**

This study has limitations with implications for interpretation of findings. First, the number of included studies was small and ROB ranged from moderate to high. As a result, we were unable to precisely estimate heterogeneity or publication bias. However, we observed a small study effect that could indicate possible publication bias. Second, estimation of means and SDs was necessary for studies with missing data which may have biased pooled effect and variance estimates. Third, our primary analysis results of pain intensity differences at baseline revealed the intervention group that received SDK had a lower baseline pain intensity score. This likely biased the results towards a favourable outcome for adjuvant SDK treatment. However, no significant baseline difference was present in the sensitivity analysis. Finally, we did not impose restrictions on dose or route of administration for SDK which may have had an effect on pooled estimates and heterogeneity.

**CONCLUSION**

In summary, adjuvant SDK was associated with a small reduction in pain intensity scores and lower opioid requirements without increased risk of serious adverse side effects. Although only small reductions in pain intensity were observed, the combination of reduced pain intensity and opioid requirements suggest the results to be clinically relevant and support the potential utility of SDK as an adjunct to opioids to treat acute pain in adult ED patients. However careful interpretation of the findings is necessary as higher quality RCTs with standardised end points are needed.

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REFERENCES


