Systematic review of the use of low-dose ketamine for analgesia in the emergency department

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ABSTRACT

Objectives: The aim of the study is to determine the performance of low-dose ketamine (LDK) as an analgesic for acute pain management in adult patients in the emergency department (ED).

Methods: We systematically reviewed electronic databases, grey literature, conference abstracts, and clinical trial registries. Two independent reviewers identified eligible studies. These selections were subsequently reviewed by one reviewer who identified the final eligible studies, using refined inclusion and exclusion criteria. Our outcome measures included the analgesic effect of LDK, need for rescue analgesia, and neuropsychological adverse events secondary to LDK use. We assessed inter-rater agreement using kappa statistics and proposed a treatment recommendation using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) software. Heterogeneity among studies precluded meta-analysis.

Results: Our electronic search identified 1,408 records; 44 were selected for full evaluation (kappa = 0.70), and 8 were included after the final review. All six randomized controlled trials and two observational studies were set in the ED where LDK was administered to adult patients (>18 years old) exclusively for pain management. All studies had an overall low risk of bias. There was extensive variation in the dose and route of LDK used (0.1-0.7 mg/kg SC/IV/IM), administration protocols, and use of adjunct analgesia. Overall, most studies reported a significant analgesic effect of LDK with occasional need for rescue analgesia and mild-to-moderate adverse events (dizziness, dysphoria, and confusion).

Conclusion: There are moderate to low quality data supporting LDK as an alternative analgesic in the ED with the potential for minimal requirement of rescue analgesia and self-limited neuropsychological adverse events.

RÉSUMÉ

Objectif: L'étude visait à déterminer l'efficacité de la kétamine à faible dose (KFD) comme analgésique dans le soulagement de la douleur aiguë chez les adultes au service des urgences (SU).

Méthode: Nous avons procédé à une revue systématique des bases de données, de la documentation parallèle, des résumés de congrès et des registres d'essais cliniques. Deux examinateurs indépendants ont repéré les études susceptibles d'être retenues, puis un examinateur les a passées en revue pour ne sélectionner finalement que les plus pertinentes après raffinement des critères d'inclusion et d'exclusion. Les critères d'évaluation comprenaient l'effet analgésique de la KFD, la nécessité d'une analgésie d'appoint et les événements neuropsychologiques indésirables du médicament. Nous avons évalué la fidélité interjuges à l'aide du test de concordance kappa, et présentons une recommandation sur le traitement qui repose sur le logiciel GRADE (Grading of Recommendations Assessment, Development and Evaluation). Il n'a pas été possible de procéder à une méta-analyse en raison de l'hétérogénéité des études.

Résultats: La recherche électronique a permis de relever 1408 études possibles, dont 44 ont été retenues en vue d'une évaluation complète (kappa = 0,70); sur ce dernier nombre, 8 finalement ont été sélectionnées après examen. Il s'agissait de six essais comparatifs, à répartition aléatoire, et de deux études d'observation menés dans des SU où la KFD avait été administrée à des adultes (>18 ans) uniquement à des fins de soulagement de la douleur. Le risque de biais était généralement faible dans toutes les études. Toutefois, il y avait des différences importantes en ce qui concerne les voies d'administration et les doses de kétamine (0,1-0,7 mg/kg, s.c./i.v./i.m.), les protocoles d'administration et la nécessité d'une analgésie d'appoint. Les études ont fait état, dans l'ensemble, d'un bon effet analgésique, nécessitant parfois une analgésie d'appoint et accompagné d'événements indésirables légers ou modérés (étourdissements, dysphorie et confusion).

Conclusions: Des données de qualité médiocre ou moyenne étayent l'utilisation de la KFD comme analgésique de rechange au SU, nécessitant dans peu de cas une analgésie d'appoint et accompagné d'événements neuropsychologiques indésirables qui disparaissent spontanément.

Keywords: analgesia, emergency department, ketamine

INTRODUCTION

Ketamine is a phencyclidine and cyclohexylamine derivative, which was initially introduced as an anaesthetic

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agent in the 1970s but soon fell out of favour as newer anaesthetic agents with limited side-effect profiles were introduced. However, ketamine has a unique ability to create a dissociative state (a trance-like cataleptic state), which preserves airway reflexes and hemodynamic stability,[1] while simultaneously providing potent analgesia, sedation, anxiolysis, and amnesia.[2] These characteristics, coupled with its relatively fast onset and offset time of action and flexible route of administration (by mouth [PO], intravenous [IV], intramuscular [IM], by rectum [PR]),[1] have made ketamine an attractive option for painful procedures requiring sedation and analgesia in the emergency department (ED).

There is ample evidence to support its use for procedural sedation and analgesia (PSA) in the pediatric population,[2] but its use in adults has been slower to gain momentum due to reports of emergence reactions (anxiety, nightmares, hallucinations, delirium).[3] Many studies outlining the use, safety, and efficacy of ketamine for PSA in the adult ED population[4-6] have led to the publication of a clinical practice guideline.[7] Despite its growing popularity as a PSA agent, ketamine's additional potential benefit exclusively as an analgesic or co-analgesic at sub-dissociative doses (<1 mg/kg IV or <2 mg/kg IM[6,8,9]) for acute pain management is a relatively new application within emergency medicine.

Pain management is an essential and challenging component of emergency medicine practice. There is a constant search for the ideal agent that will act quickly and provide almost instant analgesia with minimal side effects. Because low-dose ketamine (LDK) is a relatively new analgesic in the ED, its side effects and effectiveness as such an agent, including physician and patient satisfaction, have yet to be fully determined. The goal of this study is to systematically review the use of LDK as an analgesic or a co-analgesic for treatment of pain in the ED. We asked if, in adult patients requiring acute pain management in the ED (P), the use of LDK as an adjunct or alone (I), compared to using opioids (C), offered improved pain control, decreased the need for opioid analgesics, or decreased the occurrence of adverse events (O): *PICO*.

METHODS

This qualitative systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10]

Eligibility criteria of studies included

This qualitative systematic review studied the use of LDK in adult patients (>18 years old), requiring acute pain management for any condition in the ED. Eligible studies met the following criteria: LDK administered by any route (IV/IM/PO/SC), in any dose regimen (bolus or infusion), and compared to any opioid analgesics. LDK for analgesia is intended to be sub-dissociative and is typically defined as <1 mg/kg IV or <2 mg/kg IM.[6,8,9] The outcomes of interest were 1) analgesic effect of ketamine; 2) requirement of rescue analgesia; and 3) neuropsychiatric adverse events in patients who received ketamine. We excluded pediatric patients (<18 years of age), use of ketamine for procedural sedation, use of ketamine in a non-ED setting (inpatient, prehospital, emergency medical services), and use of ketamine for uses other than analgesia (e.g., perioperative, psychiatric, rapid sequence intubation, chronic pain).

Information sources and search strategy

We designed an electronic search strategy with the assistance of an information specialist using a combination of Medical Subject Headings (MeSH) and text words for the concepts identified in our PICO question. In February 2015, we searched MEDLINE (Ovid), EMBASE, AMED, CINAHL, and PubMed (all available records for each database since their creation up to and including February 2015). The search was limited to human studies, randomized controlled trials (RCTs), observational studies, and English language without further limitations of publication year.

We searched the National Institute of Health Trial Registry (clinicaltrials.gov), Cochrane Controlled Trial Registry, and the Cochrane database of systematic reviews. We also hand-searched abstracts from 2012 to 2014 for the Canadian Association of Emergency Physicians Conference, American College of Emergency Physicians Scientific Assembly, Society of Academic Emergency Medicine Annual Meeting, Canadian Anesthesiologists' Society Annual Meeting, and American Society of Anesthesiologists Annual Meeting. We reviewed the bibliographies of the included full-text articles for any citations that may have been missed by the electronic search strategy. We also contacted main authors to identify unpublished reports.

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Study selection

Titles and abstracts from the electronic database search results were imported into a bibliographical database library using EndNote version X7 (Thomson Scientific, Carlsbad, California). Duplicates identified by the EndNote software were automatically removed.

Two reviewers (GG, EC) independently assessed the titles and abstracts using the inclusion criteria previously described. For the initial selection, all articles with any disagreement and those that could not be decided based on title and abstract alone were included, and full texts of all of the selected articles were obtained. We calculated inter-rater agreement using kappa statistics after the initial review. The second and final selection of articles was completed by one reviewer (GG) based on a set of standardized and piloted criteria after reviewing full-text articles from the initial selection. Equivocal decisions on inclusion were reached by consensus among all investigators.

Data collection process and data items

Two data abstractors (GG, EC) created and piloted a data abstraction tool/form to ensure that this tool included all of the elements required before proceeding with standardized data extraction. This was done in accordance with the systematic-review methodology described in the PRISMA Statement.[10]

The following data were collected from studies deemed eligible after the second review: year, country and language of publication, study design, population characteristics, setting, LDK dose/route/need for re-dosing, LDK use for analgesia or procedural sedation, adjunct dose/route/need for re-dosing (e.g., opioids +/- benzodiazepines), comparator analgesic dose/route/need for re-dosing (e.g., opioids), pain score and scale used (Numerical Rating Scale [NRS]/Visual Analogue Scale [VAS]), type of pain treated, degree of pain relief, and adverse outcomes. Outcome measures recorded were analgesic effect of LDK in terms of patient-reported pain scores, "rescue" analgesia (i.e., the need for adjunctive pain management, primarily opioids, in this systematic review, to meet adequate qpain control in patients who receive only LDK) required in LDK used in analgesia, and incidence of neuropsychiatric adverse events observed in patients who received LDK. The data collection form was piloted by two reviewers.

Synthesis of results

We used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) software to estimate the strength of recommendation of each study based on the quality of evidence and bias associated with studies included in the final selection. Meta-analysis was not possible due to a large variability in reported outcome measures, dose/interval/routes of LDK used, comparator analgesic (type and dose), and indications for LDK. Hence, we performed a qualitative analysis of all of the RCTs and observational studies included in this systematic review.

Quality assessment of studies

The quality of evidence of the selected RCTs and observational studies was assessed using the Cochrane Collaboration's Tool and the GRADE software. The risk of bias in individual RCTs was assessed using the Cochrane Collaboration's Tool by analysing the outcomes of interest in six main domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. The risk of bias in individual non-RCTs was also assessed using the Cochrane Collaboration's Tool by analysing the outcomes of interest in four main domains: appropriate development of eligibility criteria, exposure/outcome measurement, confounding bias, and completeness of follow-up. These domains were used to summarize the bias in each study as low, unclear, or high.[11] This bias assessment was then extrapolated as one of the criteria for quality of evidence assessment across studies described in the following paragraphs.

The GRADE software was used to create an evidence profile that assessed and summarized the overall quality of evidence across all studies for each of the following criteria: study design, risk of bias in individual studies, inconsistency, indirectness of evidence, imprecision, and publication bias. Based on the assessment of each criterion for every study and outcome, the GRADE software generated an estimation of the quality of evidence across the studies for each outcome as "high," "moderate," "low," and "very low."

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RESULTS

Study selection and characteristics

The search strategy yielded 1,413 potential articles: 1,408 from the electronic search and 5 from grey literature. After removing duplicates, there were 1,396 articles to review. The initial review of titles and abstracts excluded 1,352 articles and yielded 44 eligible articles (kappa = 0.70; 95% CI 0.53-0.78). Thirty-eight articles were excluded for reasons indicated in the study flow diagram (Figure 1). Two eligible articles-in-press were provided directly by a main author after the initial review. Ultimately, six RCTs and two observational studies were included for the final qualitative analysis for a total of 609 patients.

General characteristics of all included studies are presented in Table 1. All articles were published in English between 1996 and 2015.[12-22] Six RCTs[12-17] included in the analysis had sample sizes from 40 to 236 and used LDK boluses of 0.15-0.30 mg/kg IV. One RCT used an infusion of 0.1 mg/kg/h IV.[15] They all used morphine boluses 0.1 mg/kg IV as a comparator. The two observational studies[18-22] included in the analysis had sample sizes from 30 to 35. They both used LDK boluses of 0.1-0.7 mg/kg IV and a variety of opioid comparators.[18-22]

Risk of bias within studies

A summary of the risk of bias assessment within individual studies is summarized in Table 2 based on the domains described in the *Methods* section. Overall, the RCTs included in the final analysis were rated to have a low risk of bias. However, we rated the RCTs to have

Table 1. Characteristics of the 8 included studies

Characteristic	Number of papers (%)
Median year of publication (range)	2011 (1996-2015)
Country of publication	
United States	5 (62.5%)
France	1 (12.5%)
India	1 (12.5%)
Iran	1 (12.5%)
Language	
English	8 (100%)
Study design	
Observational	2 (25.0%)
RCT	6 (75.0%)

RCT = randomized controlled trial.

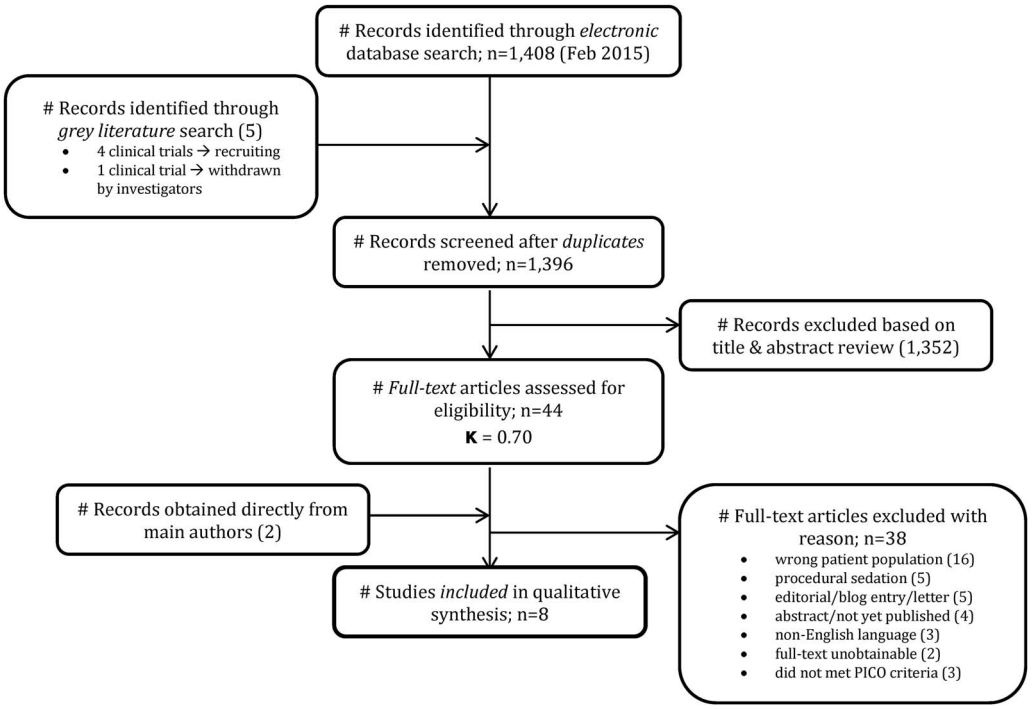

Figure 1. Study flow diagram.

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Table 2. Risk of bias assessment

RCTs (6)

						RCT bias assessment							
Study	Year	Design	Total patients	Population	Industry funding	Allocation: generation	Allocation: concealment	Blinding: participants	Blinding: assessors	Outcome: complete	Outcome: selective	Other biases
Ahmadi	2014	RCT	236	ED	No	Low	Low	Unclear	High	Low	Low	Unclear
Beaudoin	2014		60		No	Low	Low	Low	Low	Low	Low	Unclear
Galinski	2007		73		No	Low	Low	Low	Low	Low	Low	Unclear
Gurnani	1996		40		Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear
Miller	2015		45		No	Low	Low	Low	Low	Low	Low	Unclear
Motov	2015		90		No	Low	Low	Low	Low	Low	Low	Unclear

Non-RCTs (2)

						Non-RCT bias assessment			
Study	Year	Design	Total patients	Population	Industry funding	Eligibility criteria	Exposure/ outcome	Confounding	Follow-up
Ahern	2013	Cohort	30	ED	No	Low	Low	High	Low
Lester	2010	Retrospective review	35		No	Low	Low	High	Low

ED = emergency department; RCT = randomized controlled trial.

an unclear amount of bias (under "other biases") because their main outcomes (i.e., pain scores) were patient-reported. The non-RCTs had an overall low risk of bias, except for confounding bias because not all plausible prognostic factors in these observational studies were accurately measured.

Results of individual studies

Details of population, LDK dose/route, comparator analgesic dose/route, and main findings of all included studies are summarized in Table 3. The main results for each outcome are discussed in the following paragraphs.

Analgesic effect of LDK based on patient-reported pain scores

All of the RCTs compared the analgesic effects of LDK (0.15-0.30 mg/kg IV) to those of morphine (0.1 mg/kg IV), and they all concluded that IV boluses of LDK were safe and effective, either on their own or in conjunction with IV morphine for a variety of acute pain conditions seen in the ED.[12-17] They also measured pain relief in the form of patient-reported pain scores (NRS or VAS) at 30 minutes post-LDK administration, as presented in Table 4. None of the studies demonstrated a significant difference in reported pain scores at T30[12-14,17] or maximum change in pain scores[16] between the LDK and morphine groups, except for one RCT where the pain scores were consistently lower (i.e., consistently less pain) in the LDK group over a 24-hour period.[15] One RCT concluded that LDK had an opioid-sparing effect.[14]

Although the observational studies did not directly compare the analgesic effectiveness of LDK to opioids (used as adjuncts to LDK in some studies),[18,19] they concluded that LDK is a reasonable and effective option in acute pain management in the ED.[18-22] However, as indicated in Table 4, the quality of these papers was graded as "very low."

Although none of the studies observed a significant change in pain scores in patients receiving LDK (as an adjunct) at T30, they did suggest that LDK had a morphine-sparing effect[13,14] with significant analgesic effect at 5 minutes post-analgesic administration[16] and 2-hours post-analgesic administration[13] compared to morphine's analgesic effect at the same time intervals. There is a moderate level of evidence in support of using LDK as an adjunct to opioids for acute pain management in the ED.

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Table 3. Drug administration and main findings from the 8 included studies

First author (publication year)	Sample size	No. of patients who received ketamine (%)	Dose/route of ketamine	Dose/route of comparator	Main findings
RCTs n = 6)					
Ahmadi et al. (2014)	236	116 (49.0%)	0.3-0.5 mg/kg IV	Morphine 0.05-0.1 mg/kg IV	LDK has comparable analgesic effects as morphine in closed-limb fractures.
Beaudoin et al. (2014)	60	40 (67.0%)	0.15 & 0.30 mg/kg IV	Morphine 0.1 mg/kg IV	LDK at 0.3 mg/kg more effective than 0.15 mg/kg as an analgesic adjunct to morphine.
Galinski et al. (2007)	73	38 (52.0%)	0.2 mg/kg IV	Morphine 0.1 mg/kg IV	Ketamine has a morphine-sparing effect as an analgesic.
Gurnani et al. (1996)	40	20 (50.0%)	0.1 mg/kg/h SC[a]	Morphine 0.1 mg/kg IV	SC infusion of ketamine is a safe and effective analgesic in MSK trauma.
Miller et al. (2015)	45	24 (53.0%)	0.3 mg/kg IV	Morphine 0.1 mg/kg IV	LDK provided dramatic acute reduction in pain but did not last long when compared to morphine.
Motov et al. (2015)	90	45 (50.0%)	0.3 mg/kg IV	Morphine 0.1 mg/kg IV	0.3 mg/kg of ketamine provides safe and effective analgesia for acute pain.
Observational studies (n = 2)					
Ahern et al. (2013)	30	30 (100.0%)	15 mg IV	Hydromorphone 0.5 mg IV	LDK with reduced dose hydromorphone provides rapid, profound, and safe pain relief.
Lester et al. (2010)	35	35 (100.0%)	0.1-0.6 mg/kg IM/IV[b]	Varied opioid doses/routes	LDK has the potential to be used as a safe and effective analgesic adjunct.

ED = emergency department; IM = intramuscular; IN = intranasal; IV = intravenous; LDK = low-dose ketamine; MSK = musculoskeletal; RCT = randomized controlled trial; SC = subcutaneous.
[a]Initial bolus of 0.25 mg/kg IV given prior to SC infusion.
[b]Thirty out of 35 patients received IV; the rest received IM.

Rescue analgesia required with LDK

Table 5 summarizes the mean rescue analgesia dose/route and the number of patients in each group who received rescue analgesia.

In the RCT by Gurnani et al., supplemental morphine was not required at all by any patients in the LDK group.[15] Beaudoin et al. and Motov et al. reported the need for rescue analgesia as a secondary outcome.[13,17] Beaudoin et al. used morphine (0.05 to 0.1 mg/kg IV q1h) 30 minutes after initial doses were administered in each treatment arm (morphine + placebo v. morphine + 0.15 mg/kg ketamine v. morphine + 0.30 mg/kg ketamine) and did not observe a significant difference in the requirement of rescue analgesia between all three groups. Furthermore, due to the small number of patients who needed rescue analgesia, there was inadequate power to detect a difference in receipt of rescue analgesia between LDK versus morphine groups.[13]

Motov et al. administered fentanyl (1 ug/kg), if requested by patients, at 30 or 60 minutes after morphine or LDK was administered to their respective randomized group. They did not observe a statistically significant difference between the morphine and LDK groups for the use of rescue analgesia at 30 minutes (% difference = 7.0%; 95% CI -3.0 % to 16.0 %) or 60 minutes (% difference = -5.0%; 95% CI -18.0 % to 9.0 %). However, they did note that, at 120 minutes, the ketamine group required significantly more rescue fentanyl (% difference = 17.0%; 95% CI 1.0 % to 34.0 %) than the morphine group.[17]

One health record review[21] reported that a significant portion of their study patients receiving only LDK required rescue analgesia.

The low quality of all of the data for rescue analgesia is attributable to the heterogeneity in reporting the use of rescue analgesia. Ultimately, if LDK is used for acute pain management in the ED, opioids may be necessary for rescue/additional analgesia.

Incidence of neuropsychological adverse events in patients who received LDK

Because the major barrier for clinicians to use LDK over opioids is the possibility of emergence reactions, we thought it was more important to focus on adverse events specific to these emergence reactions. It is worth

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Table 4. Analgesic effect of ketamine in terms of patient-reported pain scores

Quality assessment							№ of patients in each group		Effect (VAS/NRS scores)			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LDK	Morphine	LDK (VAS @ T30)	Morphine	Quality	Importance
Pain reduction at T30 with LDK for acute pain in the ED in RCTs												
6		Not serious	Not serious	Not serious	Serious	None	283/584 (48.5%) + midaz	301/584 (51.5%)			⊕⊕⊕◯ Moderate	Primary
	Ahmadi et al.[12]						116/236 (50%)	120/236 (51%)	0.80 (SD 1.1)	0.60 (SD 1.1)		
	Beaudoin et al.[13]						40/60 (67%)	60/60 (100%)	NRS @ T30 4 (2-6)	NRS @ T30 2 (0.5-3)		
	Galinski et al.[14]						33/65 (51%)	32/65 (49%)	34.1 [95% CI, 25.6-42.6] 5	39.5 [95% CI, 32.4-46.6] 6		
	Gurnani et al.[15]						20/40 (50%)	20/40 (50%)	NRS	NRS		
	Miller et al.[16]						24/45 (53%)	21/45 (47%)	4.9 [95% CI, 5.8-4]	5 [95% CI, 6.6-3.5]		
	Motov et al. [17]						45/90 (50%)	45/90 (45%)	NRS @ T30 4.1 (SD 3.2)	NRS @ T30 3.9 (SD 3.1)		
Pain reduction at T30 with LDK for acute pain in the ED in non-RCTs												
2		not serious	serious	not serious	serious	none	705	0	LDK IV/IM @ T30		⊕◯◯◯ Very low	
	Ahern et al. [18]						30		SPID [95% CI, 21-30]	N/A		
	Lester et al. [21]						35					

CI = confidence interval; ED = emergency department; LDK = low-dose ketamine; N/A = not applicable; No. = number; NRS = Numerical Rating Scale; RCT = randomized controlled trial; SPID = summed pain intensity difference; T30 = 30 minutes; VAS = Visual Analogue Scale.

Table 5. Requirement of rescue analgesia in patients treated with LDK

Quality assessment							№ of patients requiring rescue analgesia		Mean morphine administered IV (mg/kg) (95% CI)			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LDK	Morphine	LDK	Morphine	Quality	Importance
Requirement of rescue analgesia (opioids) in RCTs												
4		Not serious	Serious	Not serious	Serious	None					⊕⊕◯◯ Low	Co-primary
	Beaudoin et al.[13]						7/20 (35%)	8/40 (20%)	4.9 mg	6.1 mg		
	Gurnani et al.[15]						0/20 (0%)	18/20 (90%)	N/A	3 mg		
	Motov et al.[17]						4/45 (9%)	1/45 (2%)	Not reported	Not reported		
							*Fentanyl *not* morphine	*Fentanyl *not* morphine				
Requirement of rescue analgesia (opioids) in non-RCTs												
1		Not serious	Serious [1]	Not serious	Not serious	None		N/A			⊕◯◯◯ Very low	Co-primary
	Lester et al.[21]						11/35 (31%)		Not reported	N/A		

CI = confidence interval; IV = intravenous; LDK = low-dose ketamine; N/A = not applicable; No. = number; RCT = randomized controlled trial.

Table 6. Neuropsychological adverse events in patients treated with LDK for analgesia

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LDK	Morphine	Relative	Absolute	Quality	Importance
Neuropsychological adverse effects – agitation, hallucinations, dysphoria, and confusion in RCTs												
6		Not serious	Not serious	Not serious	Serious	None			Not reported	Not reported	⨁⨁◯◯ Low	Secondary
	Ahmadi et al.[12]						0/116 (0%)	0/120 (0%)				
	Beaudoin et al.[13]						4/40 (10%)	0/20 (0%)				
	Galinski et al.[14]						16/33 (48%)	1/33 (3%)				
	Gurnani et al.[15]						2/20 (10%)	0/20 (0%)				
	Miller et al.[16]						9/12 (75%)	4/8 (50%)				
	Motov et al.[17]						10/45 (22%)	6/45 (13%)				
Neuropsychological adverse effects – agitation, hallucinations, dysphoria, confusion, and dizziness in non-RCTs												
2		Not serious	Serious	Not serious	Not serious	None		N/A	Not reported	N/A	⨁◯◯◯ Very low	Secondary
	Ahern et al.[18]						13/30 (43%)					
	Lester et al.[21]						1/35 (2.9%)					

CI = confidence interval; LDK = low-dose ketamine; N/A = not applicable; No. = number.

noting that there were no significant differences in respiratory depression, which is a commonly feared side effect of opioid use, between the LDK and opioid groups in all of the RCTs.[12-14,16,17]

A wide range of definitions of "neuropsychological adverse events" across all studies precluded a meta-analysis, thereby generating a "generalized" adverse event rate. The observed rate of adverse events varied from 0% to 75% of LDK cases across all eight studies. The following symptoms were analysed in this review: for the RCTs – agitation, hallucinations, dysphoria, confusion; and for the observational studies – agitation, hallucinations, dysphoria, confusion, dizziness (Table 6).

All of the RCTs except for one (in which midazolam was administered in the LDK group pre-emptively to avoid emergence reactions)[12] reported that a number of patients from the LDK group experienced some degree of dysphoria, hallucinations, agitation, and/or confusion. Galinski et al. noted neuropsychological adverse events in the LDK group but also noted that, overall, patient satisfaction was not significantly different between the LDK and morphine group.[14] One RCT with a small sample size noted that, although the LDK group experienced dysphoria, lightheadedness, hallucinations, dizziness, and/or drowsiness, midazolam was not used (part of their protocol), because there were no incidences of dissociation or emergence reactions.[16] In one RCT, there was initially a statistical difference between groups that was not sustained at 15 and 30 minutes post-injection.[17] Another RCT reported that only 2 out of 40 patients experienced "dreams" after the initial bolus dose of ketamine, which was statistically insignificant.[15]

A significant portion of patients in the prospective cohort study by Ahern et al. experienced neuropsychological adverse events that were "self-limited psychomimetic side effects."[18] In the other retrospective case series, 1 patient out of 35 reported having "brief mild dysphoria"[21] but no other dangerous adverse events.

There is a moderate level of evidence reporting low incidence neuropsychological side effects, therefore supporting the use of LDK for analgesia in the ED.

DISCUSSION

Summary of evidence

The objective of this study was to systematically review the use of LDK (0.15-0.30 mg/kg IV) as an analgesic or co-analgesic for the acute pain management of adult

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patients in the ED. Our findings are summarized as follows: 1) LDK has an inconsistent but potentially rapid onset of analgesic effect. Although short-lived, this quick analgesic effect often reduces the required doses of opioids for adjunct analgesia; 2) patients receiving only LDK for pain management may require administration of rescue analgesia in the form of opioids to adequately control their pain; and 3) neuropsychological adverse effects of LDK are often self-limited, not life-threatening, with no significant emergence reactions reported out of 609 patients in the studies included in this review. Our findings suggest that LDK is a relatively safe and opioid-sparing alternative for acute pain management in adult patients in the ED.

A similar systematic review and meta-analysis by Lee et al.[23] that also focused solely on the use of LDK for acute pain has three major differences compared to this review. Firstly, Lee et al.[23] included two RCTs by Messenger et al. and Jennings et al. that were excluded in this review based on our clearly defined PICO. The RCT by Messenger et al.[4] included patients over the age of 16 years, whereas our inclusion criteria was for a population over age 18 years. The RCT by Jennings et al.[24] was excluded based on setting; it was conducted out-of-hospital and not in an ED. Secondly, given the grossly heterogeneous data, we believed that a meta-analysis was not justifiable and that a narrative review was the only methodologically sound way of reporting our findings. Thirdly, Lee et al.[23] used two reviewers for study selection and data extraction. Two reviewers were involved in our study selection process, and the data were extracted by one reviewer only. All study results were obtained directly from the reviewed articles and were not subject to interpretation, thereby mitigating the need for the data to be extracted separately by two reviewers.

A few limitations of the review by Lee et al.[23] are also worth noting: 1) They failed to define a clear PICO, hence their reason for the inclusion of the RCT by Jennings et al.,[24] but exclusion of other out-of-hospital studies is unclear; 2) our methodology is more robust – explicit inclusion/exclusion criteria and thorough search methods; and 3) we used the GRADE software to assess quality of evidence and risk of bias in each study.

In 2015, a review of four RCTs by Sin et al.[25] (three adult and one pediatric; two of the four RCTs are included in our review,[14,15] whereas the other two were ineligible for our review) showed no detectable differences in pain scores between the analgesic effect of LDK and opioids. They concluded that LDK could produce satisfactory pain control and could be opioid-sparing. Furthermore, adverse events resulting from LDK use were limited and did not require any intervention.[25] Emergence phenomenon was reported in one patient in the pediatric RCT.[26]

Another RCT by Messenger et al. in 2008, which was excluded in our review due to its inclusion of pediatric patients, concluded that 0.3 mg/kg IV "sub-dissociative dose" of ketamine is safer than fentanyl plus propofol in PSA. Also, no emergence reactions were observed, which was attributed to the small sample size and LDK by the original study authors.[4]

LIMITATIONS

This systematic review has a few limitations that we wish to acknowledge. Firstly, there was a single reviewer for the final inclusion criteria. However, this limitation is mitigated by stringent predetermined inclusion/exclusion criteria. Secondly, the strength of recommendation regarding the adverse effects of LDK was limited by the small number of papers (and small sample sizes within each study) reporting such an outcome. Thirdly, only neuropsychological adverse events were analysed and reported in this review, so it is important to note that other side effects, such as respiratory depression and gastrointestinal symptoms, may still be seen with LDK.

CONCLUSIONS

Our findings, despite being derived from moderate to very low levels of evidence, suggest that LDK could be considered as an effective and opioid-sparing adjunct with some risk for neurophsychological side effects in acute pain management in the adult patients in the ED.

There is an opportunity for a well-conducted RCT with a larger sample size and rigorous methodology to further elucidate the true extent of LDK's neuropsychological side effects and analgesic profile for acute pain in the ED.

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SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/cem.2017.48

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