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Intranasal ketamine as an analgesic agent for acute pain management in emergency department: A literature review

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ABSTRACT

Ketamine is a well-known dissociative anesthetic agent, and has been used over 50 years. Intranasal pathway is a mucosal way for absorbing agents to directly affect in brain via olfactory sheets, bypassing first pass metabolism and the blood brain barrier. The current uses of intranasal ketamine as an analgesic agent for acute pain management in emergency department are discussed in this review article. Using "ketamine", "pain or analgesia", and "intranasal" as keywords, a search of google scholar, Pubmed, web of science, and Medline database from 1970 until 2017 was performed. Finally, from 1 204 papers extracted *via* primary search, 1 088 papers were omitted and finally 10 studies were considered for further assessment. There were four observational studies, one case series and report and 5 clinical trials. Ketamine was used for acute pain control due to musculoskeletal trauma, burns, and painful procedures. A total of 390 cases were included in these studies. The studies used ketamine with doses ranging 0.45-1.25 mg/kg *via* intranasal pathway. Intranasal ketamine provides relatively rapid, well tolerated, and clinically significant analgesia for emergency department patients. Considering the lack of adequate studies and undetermined intranasal dose, it is better to conduct further high quality investigation in both adults and pediatrics.

1. Introduction

Ketamine is a well-known dissociative anesthetic agent that mediated its effects mainly *via* blockade of N-methyl-D-aspartate and hyperpolarisation-activated-cyclic-nucleotide receptors[1]. For over 50 years, it has been used in various ways[1-3]. It is likely that it is a very useful agent for conducting procedural sedation and analgesia in emergency department (ED)[4-6]. Despite using as an

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analgesic agent in management of chronic pain, but it is not routinely used for acute pain management of ED due to its potentially side effects such as dissociation and emergence phenomenon[7,8]. Due to overcrowding and lack of human and facilities resources in EDs, using a safe drug with minimal side effects is crucial. Recent evidence proved efficacy of low dose ketamine in this regards, although it needs further investigation[9-11]. Each drug has some different pathway of administration. Intranasal pathway is a mucosal way for absorbing agents to directly affect in brain *via* olfactory sheets, bypassing first pass metabolism and the blood brain barrier[12]. Accordingly, the current uses of intranasal ketamine as an analgesic agent for acute pain management of ED are discussed in this review article.

2. Evidence acquisition

All observational and randomized controlled trials that surveyed the use of intranasal ketamine as an analgesic agent in the emergency setting were eligible for assessing in this study. Using "ketamine", "pain or analgesia", and "intranasal" as keywords, a search of google scholar, Pubmed, web of science, and Medline database from 1970 until 2016 was performed. The searching process was performed with two independent investigators. All papers and additional references from their citation were also included. Initially the abstracts were screened regarding the use of intranasal ketamine as an analgesic agent for acute pain management in both prehospital and ED setting. No age limit was considered and both adult and pediatric studies were included. Papers that used ketamine through other pathway than intranasal published in non-English languages, animal studies, and review articles were excluded. Non-available full text, duplicated studies, and unpublished ones were eliminated. Evaluation was performed independently by 4 reviewers and validated scales were using pain measurement tools and also mentioning side effects were in the studies. The results were summarized and presents in Tables.

3. Results

Finally, from 1 204 papers extracted *via* primary search, 1 088 papers were omitted and finally 10 studies were considered for further assessment. There were four observational studies, one case series and report and 5 clinical trials including 4 randomized, 1 non-randomized, 4 blinded, and 1 non-blinded one (Figure 1). Ketamine was used for acute pain control due to musculoskeletal trauma, burns, and painful procedures. A total of 631 cases were included in these studies. The studies used ketamine with doses ranging 0.45 - 1.25 mg/kg *via* intranasal pathway.

Table 1 shows the characteristics and summery of the clinical trial studies included in the current review. Clinical trial studies showed acceptable analgesia with ketamine with no differences compared with other analgesic agents[13-15]. Table 2 shows the characteristics and summery of the non-clinical trial studies included in the current review. The observational studies and case reports concluded analgesic effect of ketamine without major side effects[19-22]. Summary of reported side effects in the studies included in the current review were reported in Table 3. All side effects were minor and transient.

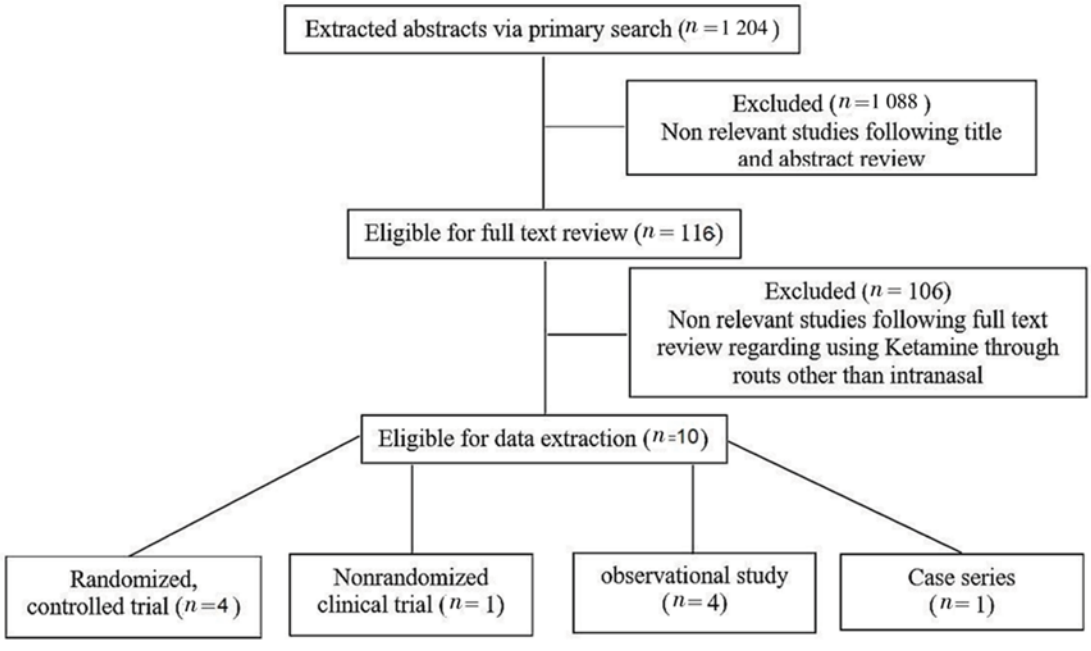

Figure 1. Fowchart of search strategy and paper extraction in current review.

Table 1

Characteristics and summery of clinical trial studies in current review.

Ref	Design	Participants	Analgesia agents	Outcome	Result	Conclusion
Graudins *et al*[14]	Randomized, controlled, double-blind trial	A total of 80 children aged 3 to 13 years and weighing less than 50 kg, with isolated limb injury and pain of more than 6/10.	IN ketamine (1 mg/kg) or fentanyl (1.5 microgram/kg). coadministered oral ibuprofen at 10 mg/kg	Median pain reduction at 30 min; pain reduction at 15 and 60 min, subjective improvement and satisfaction, University of Michigan Sedation Score, adverse events, and rescue analgesia.	Pain reductions of ketamine *vs* fentanyl; 45 *vs.* 40 mm, respectively (95% *CI* 10 to 20 mm).	IN fentanyl and ketamine had similar analgesic effect in children with limb injury. Ketamine had more minor adverse events.
Nejati *et al*[15]	Prospective double-blind randomized clinical trial	72 stable subjects aged >18 years who required NG tube placement for diagnostic or therapeutic purposes in the ED	Local ketamine plus water-soluble lubricating gel and water-soluble lubricating gel alone	VAS fallowing of NG tube placement was measured; evaluate the difficulty of the procedure using a 5-point Likert scale.	VAS of the ketamine *vs.* control groups (19.03± 3.56 *vs*. 33.33±5.31), not statistically different between the two groups (2.39±1.25 *vs.* 2.78±1.56).	IN ketamine is an effective agent in reducing pain during NG tube insertion among patients without serious underlying illness.
Nielsen *et al*[16]	Prospective nonrandomized open-label clinical trial	50 child 10 kg candidate for a painful procedure	Formulation of IN sufentanil 0.5 mcg/kg- ketamine 0.5 mg/kg	Pain intensity before and during the procedure was measured using age-appropriate pain scales.	Procedural pain intensity scores 5 (0-10) in 78% of the painful procedures.	Sufentanil/ketamine nasal spray provided rapid onset of analgesia for a variety of painful procedures.
Reynolds *et al*[17]	Randomized controlled,	87 child (4-17 years old) suspected isolated fractures	1 mg/kg IN ketamine *vs*. 1.5 µg/kg IN fentanyl	Frequency of cumulative side effects and adverse events within 60 min of drug administration and difference in mean pain score reduction at 20 min.	Cumulative number of side effects was 2.2 times higher in the ketamine group, but there were no serious adverse events.	IN ketamine was associated with more minor side effects than IN fentanyl. Pain relief at 20 min was similar between groups.
Parvizrad *et al*[18]	Balanced block randomized controlled	154 adult patients with isolated orthopedic trauma and VAS 60 mm	Ketamine-IN (0.4 mg/kg IN ketamine and an equal volume of placebo saline IV and ketamine-IV (0.2 mg/kg ketamine IV with 0.5 mL saline IN)	Patients were assessed for VAS measurement and adverse events At 5, 10, 20, and 30 min.	No difference between two groups in case of score change of VAS and Adverse events in both groups were mild and transient.	IN ketamine is may be used in cases where there is no need for venipuncture of peripheral vessels, especially in crowded EDs.

VAS: visual analog scale; IN: Intranasal; IV: intravenously.

Table 2

Characteristics and summery of non-clinical trial studies in current review.

Ref	design	Participants	Analgesia agents	Outcome	Result	Conclusion
Andolfatto *et al*[19]	Prospective observational study	40 patients aged >6 years old (mean age 47 years) with primarily orthopedic injury	0.5 to 0.75 mg/kg intranasal ketamine	Clinical significant VAS reduction (13 mm) within 30 min, mean reduction of VAS, median time require to achieve at least 13 mm reduction of VAS, vital sign change, side effects.	Median changes in VAS at 30 min: 34 mm (44%).	Reduced VAS pain scores to a clinically significant degree in 88% of ED patients without major side effects.
Yeaman *et al*[20]	Prospective, observational study	72 patients (median aged 34.5 years) with severe pain; VAS 6.	Ketamine 0.7 mg/kg intranasal (first 6 mo); 1.0 mg/kg intranasal (second 6 mo) followed by a 0.5 mg/kg intranasal (15th min) if no pain reduction	Change in VAS at 30 min; patients with clinically significant VAS reduction in VAS (20 mm) at 30 min; significant pain reduction dose of ketamine.	Median reduction VAS at 30 min was 24 mm (IQR: 2-45). Significant VAS reduction 20 mm in 40 cases (56%, 95% *CI*: 44.0-66.7). Total median ketamine dose was 0.94 mg/kg (IQR: 0.72-1.04).	Intranasal ketamine of 1 mg/kg, was an effective analgesic agent in 56% of study patients. Needs further investigation in adults.
Yeaman *et al*[21]	Observational study	28 patients aged 3-13 years, with moderate to severe (6/10) pain from isolated limb injury	Ketamine intranasal	Change in median VAS at 30 min. change in median pain rating at 60 min, patient/parent satisfaction, need for additional analgesia and side effects.	Median VAS decreased from 74.5 mm (IQR 60-85) to 30 mm (IQR 12-51.5) at 30 min.	An average dose of 1.0 mg/kg intranasal ketamine result in adequate analgesia by 30 min.
Shrestha *et al*[22]	Cross sectional, observational study	39 patients aged > 8 years old with various acute injuries and VAS pain score >50 mm	Ketamine 0.7 mg/kg intranasal with an additional dose at 15th minutes (0.3 mg/kg) if VAS >50 mm	Number of patients achieving 20 mm reductions in VAS at 15 min; median reduction in VAS at 15, 30 and 60 min, changes of vital signs, adverse events, satisfaction of patients, and need for additional ketamine.	VAS reduction from baseline to 40 mm (IQR 20–40), 20 mm (IQR 14–20) and 20 mm (IQR 10–20) respectively at 15, 30 and 60 min.	Intranasal ketamine is an analgesic choice for patients with acute injury in moderate to severe pain in an overcrowded and resource limited ED.
Johansson *et al*[23]	Case series	9 patients with trauma in outdoor winter-conditions	S-Ketamine 0.45-1.25 mg/kg.	----	Initially median pain-score from median 10 (interquartile range 8–10) and a finally median pain-score after was 3 (interquartile range 2–4).	Nasal administration of S-ketamine is off label and as such we only use it as a last resource and propose that the effect and safety of the treatment should be further studied.

VAS: visual analog scale.

Table 3

Summery of reported side effects in studies of current review.

Ref	Side effects
Graudins *et al*[14]	Adverse events, mainly mild, were reported for ketamine by 78% of patients.
Nielsen *et al*[16]	The reported adverse effects were mild and mostly related to an unpleasant bitter taste (15/50) immediately after administration of the nasal spray; Three events of vomiting occurred
Andolfatto[19]	All adverse effects were transient and did not require treatment; There were no changes in vital signs requiring clinical intervention.
Yeaman *et al*[20]	Seventy-nine per cent of subjects (57/72) reported 96 adverse effects, the most common being dizziness (31.9%).
Yeaman *et al*[21]	A total of 28 reported adverse events were all transient and mild.
Shrestha *et al*[22]	Adverse events were generally mild and transient in nature, resolving mostly within 60 minutes after administration of ketamine

4. Discussion

Based on the findings of current review, there are acceptable analgesic effects for intranasal ketamine. However, since all studies were included without consideration age, clinical situation and dosage, it would not be possible to determine definite evidence regarding use of intranasal ketamine as an analgesic agent for acute pain management of ED.

Bioavailability of ketamine through intranasal pathway is 45%-55%[13]. It was reported that intranasal ketamine is detectable in blood 2 min after administration and its maximum concentration would be at 30 min later, and provides sufficient analgesia up to 1 h[24]. When used in combination with other drugs, low dose intranasal ketamine could result in reducing the dose of the other agents. It is particularly useful in opium-addicted patients[14,20,21,25]. Co-administration of other analgesic agents such as in the study of Graudins *et al* that patients received ibuprofen, it may be affected on study results[14].

All studies were conducted on traumatic patients, and supported intranasal ketamine sufficient analgesic effect 30 min later, although available data regarding its use in adult is still limited[14-22,16,23]. Clinical trials showed no difference between the studied groups regarding pain control. Reported side effects were minor and transient and did not need any intervention[14-16].

Ketamine was used for painful procedural sedation. Nejati *et al* showed that intranasal ketamine facilitated nasogastric tube insertion, without increasing the rate of vomiting[15]. In the study of Neilsen *et al*, sufentanil/ketamine nasal spray provided rapid onset of analgesia for a variety of painful procedures, so intranasal ketamine is an acceptable choice for suturing, intravenous line insertion and *etc*[16].

There were some differences among studies regarding how the drug was administered into nostril, dripping with a syringe or using a spray device. Better absorption occurs while the agent is sprayed into nasal cavity that provided wider mucosal surface area for absorption[19,22].

Nasal ketamine may be used in cases where there is no need for venipuncture of peripheral vessels, especially in crowded EDs and in prehospital situation, where venipuncture is difficult[18,26].

The authors believe that intranasal ketamine is safe and does not need close monitoring, but in cases with severe pain in crowded ED it may be not suitable or possible to wait 30 min to achieve sufficient analgesic effect. Use of ketamine in combination with low dose of other analgesic agents would be a better decision. Intranasal pathway is a rapid and needleless approach that decline the risk of transmission of blood-borne infections in a stressful situation of out of hospital such as bad weather condition and dangerous environment, as well in cases that have not an intravenous access or does not need to insert intravenous line like an isolated orthopedic trauma, intranasal rout would be preferable.

5. Conclusion

Intranasal ketamine provides relatively rapid, well tolerated, and clinically significant analgesia for ED patients. Considering the lack of adequate studies and undetermined intranasal dose, it is better to conduct further high quality investigation in both adults and pediatrics.

Conflict of interest statement

The authors report no conflict of interest.

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