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Original Contribution

Intranasal ketamine reduces pain of digital nerve block; a double blind randomized clinical trial☆

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ABSTRACT

Background: Low dose ketamine can be used as analgesic in acute pain management in the emergency department (ED).
Objective: Efficacy of IN ketamine in acute pain management in the ED.
Method: This is a double blind randomized clinical trial on patients older than 15 years who needed digital nerve block (DNB). Participants randomly received IN Ketamine (1 ml = 50 mg) or placebo (normal saline, 1 ml) 5 min before DNB. In both groups, patients' pain score was recorded by visual analogue score (VAS) at baseline, after DNB and 45 min after completion of DNB. Adverse effects of ketamine and changes in vital signs were also recorded and compared with placebo group.
Results: A total number of 100 patients were enrolled in the study with the median (IQR) age of 36.5 (26) years, including 65 men and 35 women. IN ketamine resulted in less pain compared to placebo after performing DNB and 45 min after the procedure. Median (IQR) basic VAS score was 50 (15) in ketamine group, and 49 (27) in control group. Median (IQR) block pain VAS score was 28.5 (19) in ketamine group and 47.5 (31) in control group. Median (IQR) procedural pain VAS score was 21.5 (16) in ketamine group and 43.5 (29) in control group. Only 7 patients had adverse effects in either group.
Conclusion: The findings of this study suggest that IN ketamine can be effective in reducing pain in patients with acute pain, without adding significant side effects.

1. Introduction

Acute pain management, including reduction of procedural pain, through an effective, available, fast acting, easy-to-administer method with minimum side effect is of paramount importance in the emergency department (ED). Digital nerve block (DNB) is a painful procedure and one of the most commonly performed techniques in the ED [1]. Pain control during DNB gives the patient and the physician confidence and comfort.

An *N*-methyl-D-aspartate receptor antagonist, ketamine, is widely used as an analgesic agent for treatment of acute pain in different clinical settings [2,3]. Due to its lipophilic structure, ketamine easily passes the blood-brain barrier and inhibits central perception of pain [3]. Ketamine at doses >1 mg/kg has been used as a dissociative anesthetic. Furthermore, low-dose ketamine (<0.3 mg/kg) may also be used to control perioperative pain or chronic pain as adjunctive analgesia [4]. Ketamine is used via different routes. It has been suggested that intranasal (IN) form of this drug can provide an efficient, painless and well tolerated analgesia for up to 60 min [3]. The results of recent studies on the analgesic effect of IN ketamine are controversial [4,5]; most have demonstrated adequate analgesia [5,6] and some have shown a relatively low response rate [4]. Common to all these studies was that their participants had different types of injury and the procedures (in case of analgesia for painful procedures) were performed by different operators, which might have affected the findings.

We designed this study to evaluate whether intranasal ketamine can be effective in reducing pain during painful procedures in ED. We selected DNB as the painful procedure in all subjects in our study and by having the procedure performed by a single operator tried to avoid the potential confounder of various pain severities of the procedure [7]. We also assumed that studying only patients with finger injury would help us minimize the variation in baseline pain severity of the

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patients. We believe that these two measures, not used in previous studies, can increase the validity of our findings.

2. Methods

This randomized double blind clinical trial was conducted to assess the efficacy and safety of IN ketamine as an analgesic drug for acute pain. The study protocol was approved by the university ethical committee.

2.1. Study setting and population

The study was conducted at a university-affiliated tertiary care hospital with 1000 floor beds and 50 emergency beds. The ED is staffed 24/7 by board certified emergency physicians and has an annual census of 75,000 patients. Approximately 2000 DNBs are done per year in our ED. The study took place between Januarys 2014 and October 2014.

All adult (>18 years) patients who presented to the ED and required DNB were eligible for this study, provided that they did not have any exclusion criteria. The exclusion criteria are presented in Table 1 [8].

2.2. Study material

Ketamine Hydrochloride and normal saline were used in the study. The 2-ml syringes were used to dispense the medications.

2.3. Study protocol

Using a convenience sampling approach, during the clinical shifts of one of the researchers (F.T.S.), all patients presenting to the ED who met the inclusion criteria and lacked the exclusion criteria were approached and the intent of the study was explained to them. They were enrolled in the study if they granted written informed consent.

All participants were assessed regarding their pain severity using a standard 100-mm visual analogue scale (VAS) [9] by asking them to mark the pain severity along the scale. We also measured and recorded their vital signs including oxygen saturation at room air (O_2Sat), pulse rate (PR) and blood pressure (BP).

The patients were then randomized using a computer generated random sequence of blocks of four by one of the investigators (A. N.). Allocation concealment was achieved using sealed envelope technique. A pack of sequentially number sealed envelopes containing identical appearing 2 ml-syringes (either 1 ml of ketamine or 1 ml of normal saline) was available to the investigator. They investigator instilled either 1 ml (50 mg) of ketamine or 1 ml of normal saline (placebo) into the patient's nostril. After 5 min, standard dorsal web space DNB [10] was performed by one of the researchers (F.T.S.). Then, the patient's pain score was assessed and recorded. The required procedure then followed at the discretion of the treating physician. Forty-five minutes after the DNB, VAS was reassessed. The patients were monitored during the procedure and for 60 min after its completion. Adverse effects were recorded if reported by the patient or the treating physician. Vital sign (O2 Sat at room air, PR and BP) were also measured and recorded. All measurements were performed by a trained research assistant but the results were not hidden from the treating physician or the operator. The patient was not reminded of his/her previous pain score. Participants, the researcher who enrolled the patients, the operator who conducted DNB, those assessing baseline data and outcomes, and the person who performed statistical analysis were all blinded to the nature of the medication that the patients received.

Table 1
Exclusion criteria for participation in the study.

1. Altered mental status
2. Signs or symptoms of decompensated heart failure
3. Pregnancy
4. Poorly controlled hypertension (systolic BP > 180 mm Hg or diastolic BP > 90 mm Hg)
5. Known history of coronary artery disease
6. Recent history of transient ischemic attacks in last year
7. History of stroke or cerebral aneurysms
8. Dementia
9. Reactive airway disease
10. Sinus/nasal anomalies or dysfunction (active suppurative rhinitis)
11. Allergy to ketamine, allergy to lidocaine
12. Dextromethorphan usage
13. Chronic opium use
14. Recent use or prescription of any type of narcotic in last 24 h
15. Uncooperative patients (insurmountable language barrier)
16. Multiple trauma patients

2.4. Outcome measures

The primary outcome was reduction in pain intensity. Secondary outcomes included the occurrence of adverse effects and complications within 1 h upon completion of the procedure.

2.5. Statistics analysis

Considering a standard deviation of 28 in pain scores (obtained through a small pilot study) and an effect size of 16, we calculated a sample size of 49 in each group to reach a power of 80% (beta = 0.2) and a risk of type I error of 5% (alpha = 5%). We decided to enroll 50 patients in each group.

All data was entered into an Excel spreadsheet and analysis was performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). For continuous variables and frequency distribution of categorical variables, data was reported as median (±IQR) or mean (±SD) using descriptive statistics. Mann-Whitney *U* test and Sign test were used for comparing continuous variables, and Pearson χ^2 test with Fisher's exact test was used for assessment of categorical variables. *P*-value < 0.05 was considered statistically significant.

3. Results

The flow of the participants in this study is illustrated in Fig. 1.

Table 2 illustrates the baseline characteristics of the participants. As can be noted, there is no significant difference between the two groups regarding their age, sex and injury type.

Participants' pain scores at baseline (VAS1), after DNB (VAS2) and 45 min after completion of DNB (VAS3) have been compared in the control and intervention groups and presented in Table 3. It can be seen that VAS2 and VAS3 are significantly different between the two groups.

Vital signs, at baseline and after 1 h, were not significantly different between the ketamine and placebo groups (Table 4).

Table 5 shows the frequency of adverse effects in each group. Few adverse events were reported in either group but there was no need for physician intervention. There was no statistically significant difference between the two groups in terms of the frequency of unwanted effects.

4. Discussion

The results of this randomized clinical trial revealed that administration of intranasal ketamine in patients who underwent a painful procedure resulted in a significant reduction in procedural pain as well as pain experienced 45 min after the block.

Although initially introduced as an anesthetic agent in 1960, ketamine has gained growing popularity for newer applications, especially in the ED settings. Low sub-dissociative dose of ketamine (<1 mg/kg) has recently been considered as an analgesic agent for acute pain management [11]. It exerts analgesic effects through blocking pain perception and peripheral pain signaling [8] and offers the advantage that the patients remain completely awake and alert during analgesia. This makes ketamine a good choice for controlling acute pain in the ED.

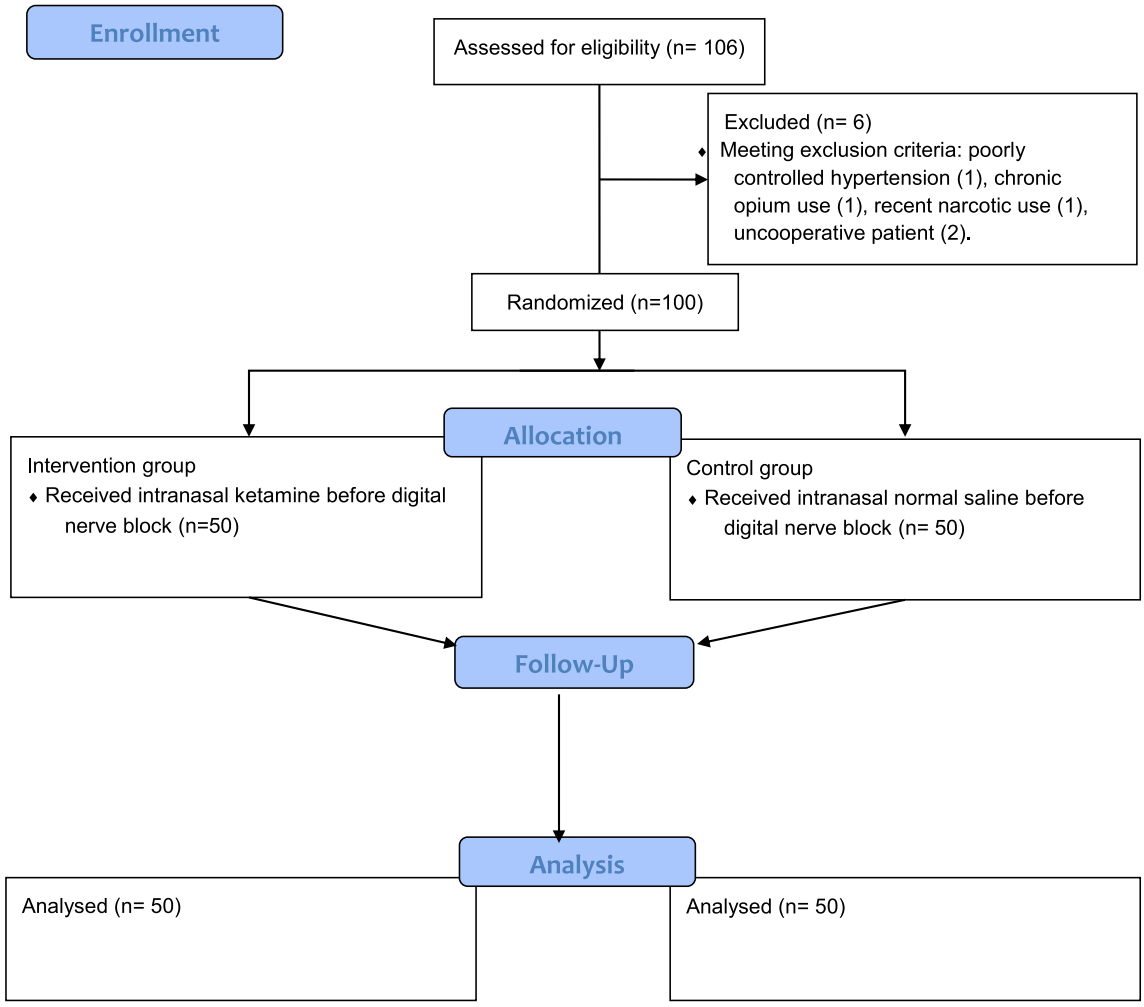

Fig. 1. Flow chart of participants in the study.

Ketamine has different routes of administration (Intravenous, Intramuscular, Oral, or IN). Intravenous route is preferred but not always feasible in the ED. IN administration of ketamine is a convenient option with rapid systemic absorption and ease of access [12]. It is effective, safe, well-tolerated, and allows a rapid absorption of the drug into bloodstream [13,14]. The analgesic effect of IN ketamine begins within 10 min reaches its peak in 10 to 14 min is. Its long recovery time, in comparison with other medications such as propofol, makes it suitable for longer procedures such as abscess drainage or wound closure [15]. IN ketamine can be administered by mucosal atomizer device or, when atomization device is not available, by drops, with similar effects [16].

In our study the same painful procedure (DNB) was performed by a single operator in all patients; so the significant pain reduction observed in our patients can be attributed to IN ketamine. DNB is one of the common procedures conducted in the ED [1]. Several methods [17] have been used to decrease the discomfort of the injection including local ice [18], topically applied analgesics, needleless injection systems and vapocoolants [19]. Use of ketamine before DNB may be a viable option for patients fearing from needle injection or patients who require painful manipulation for fracture replacement, abscess drainage, nail repair or other painful procedures.

In this study we also assessed ketamine side effects and any changes in vital sign. Fortunately, the incidence of adverse effects was negligible and they were self-limited and did not necessitate physician intervention.

In an observational study in 2013, Yeaman et al. examined the effectiveness of IN ketamine as an analgesic on 26 children (3–13 years) with

Table 2
Baseline characteristics of the participants in intervention and control groups.

Characteristic	Ketamine group ($n = 50$)	Placebo group ($n = 50$)	P value
Age in years median (IQR)	39 (25)	31 (24)	0.1
Sex (n, %)			0.3
Male	31, 62	34, 68	
Female	19, 38	16, 32	
Injury type (n, %)			
Laceration	43, 86	40, 80	0.6
Fracture	3, 6	6, 12	
Abscess	3, 6	2, 4	
Dislocation	1, 2	2, 4	

Table 3
Participants' pain scores at base line, after DNB and 45 min after DNB in the intervention and control groups.

	Ketamine group ($n = 50$)			Placebo group ($n = 50$)			P value[b]
	Median	IQR	95% CI[c]	Median	IQR	95% CI	
VAS[a] 1 (basic pain)	50	15	(42.5–53)	49	27	(47–58)	0.19
VAS 2 (block pain)	28.5	19	(24–32)	47.5	31	(40–51)	<0.001
VAS 3 (45 min after DNB)	21.5	16	(17–25)	43.5	29	(32–42)	<0.001

[a] VAS: visual analogue scale.
[b] Mann-Whitney U test.
[c] CI: confidence interval.

Table 4
Participants' vital signs before and 1 h after the procedure in the intervention and control groups.

Vital sign	Time zero			After 1 h		
	Ketamine ($n = 50$)	Placebo ($n = 50$)	*P* value	Ketamine ($n = 50$)	Placebo ($n = 50$)	*P* value[a]
Pulse rate (bpm)	81.6 ± 14	84.9 ± 10.9	0.1	79.6 ± 11.4	81.9 ± 11.2	0.3
Blood pressure (mm Hg)	119.5 ± 11.2	121.9 ± 14.9	0.3	119 ± 11.3	122.4 ± 19.8	0.2
Oxygen saturation (%)	95.8 ± 1.4	96 ± 1.6	0.6	95.7 ± 1.5	96 ± 1.6	0.4

[a] Fisher's exact test.

isolated limb injury. In their study, only 8 patients needed additional opioid analgesia and all adverse events were transient [8].

In a systematic review in 2017 IN administration of ketamine for procedural sedation and analgesia in children was reviewed. IN ketamine provided adequate sedation to perform procedures but small sample size and failure to compare IN ketamine with IV sedatives were mentioned as limitations of these studies [20].

In a double-blind randomized clinical trial, Nejati et al. showed that IN ketamine reduced pain severity in patients undergoing nasogastric tube insertion as compared to sterile water [21]. The most common adverse effects in ketamine group were reported to be nausea/vomiting and cough. No significant change in vital signs was stated in either group [21].

In 2016, in a cross sectional, observational study on patients older than 8 years old with acute moderate to severe pain, IN ketamine was used as an analgesic [22]. Reduction in VAS scores was significant in the studied patients. Dizziness was the main unpleasant effect in this study and no critical changes in vital signs were noted [22]. In this study, the operators were not blinded to the drug and ketamine was not compared with placebo.

In 2016, analgesic application of ketamine was evaluated [23] in a cohort of ED patients with acute pain (multiple trauma, oncology pain, abdominal pain, etc.). Administration of low doses ketamine was shown to be effective in pain reduction. Feeling weird and anxious were the only adverse effects, and vital signs were maintained. The result of this study was similar to ours but the sample size was small and the baseline pain was not similar in patients.

Carr et al. [8] studied the efficacy of IN ketamine for the treatment of breakthrough pain in patients with chronic pain. Ketamine group had significant lower intensity of pain compared to placebo group after 10 min and lasting up to 60 min. Unlike our study, baseline pain was not the same in all cases. The investigators reported nasal irritation, transient change in taste and two cases of transient elevation in blood pressure but none of them were significant.

Some studies [21,23] evaluated the adverse effects of ketamine in procedural sedation. No serious adverse events were reported. Transient agitation, recovery agitation, vomiting, and hypersalivation were the main side effects, among which recovery agitation needed treatment with benzodiazepine.

4.1. Limitation

Our study is a randomized, double blind controlled trial in which a single operator performed all the procedures. This makes the comparison between the pain scores in the two groups more accurate. However, our study faces several limitations which must be acknowledged. Firstly, it was a single-center low-population study, conducted in a tertiary care hospital. Reproducing the study on a larger sample sizes will improve its generalizability. Secondly, since all nerve blocks were performed by one operator, we could not be sure if the pain would be similar if other physicians had done the procedure.

Table 5
The frequency of adverse effects in the intervention and control groups.

Side effect	Ketamine group ($n = 50$)	Control group ($n = 50$)	*P* value
Nausea	3 (6%)	2 (4%)	>0.05
Vomiting	1 (2%)	0	>0.05
Cough	0	1 (2%)	>0.05
Feeling anxious	1 (2%)	0	>0.05
Total	4[a] (8%)	3 (6%)	0.9

[a] One patient had both nausea and vomiting.

5. Conclusion

IN ketamine can effectively lower reported pain in patients undergoing painful procedures such as DNB. Side effects are trivial and improve spontaneously.

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