

Efficacy of intraoperative subanaesthetic dose of ketamine on post-operative analgesia for patients undergoing single level lumbar discectomy under general anesthesia: A placebo control randomized clinical study



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ABSTRACT

Background: Sub-anesthetic ketamine is becoming increasingly popular for opioid sparing analgesic properties. **Aims and Objectives:** This study was done to determine the efficacy of intraoperative infusion of sub-anesthetic dose of ketamine on post-operative analgesia in single level lumbar discectomy surgeries. **Materials and Methods:** A prospective, randomized, and control study was carried on 60 patients of American Society of Anesthesiologists I and II aged between 18 and 65 years undergoing single level lumbar discectomy under general anesthesia. After induction of anesthesia, Group A received Ketamine 0.3 mg/kg intravenous (IV) bolus followed by infusion at 4 µg/kg/min and Group B received 0.9% saline bolus dose of similar volume and infusion was started at similar rate. Post-operative pain relief, opioid sparing effect, and side effects if any were recorded. **Results:** There was significant difference ($P < 0.001$) in post-operative Numeric Rating scores for initial 6 h in Group A patients compared to Group B and prolonged duration of analgesia (8.5 vs. 4.25 h) along with reduced postoperative tramadol consumption. **Conclusion:** In lumbar spine discectomy, intraoperative ketamine infusion at sub-anesthetic doses produces more effective post-operative analgesia along with opioid sparing effect without any side effects.

Key words: Ketamine; Lumbar discectomy; Postoperative analgesia; Sub-anesthetic dose

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INTRODUCTION

Patients with spine disorders usually present with chronic back pain. They would have usually received multiple pain medications and management of post-operative pain in these patients is a clinical challenge. Patients undergoing spine surgeries often have severe post-operative pain because of extensive injury of muscles, bones, and soft tissue. Inappropriate pain relief can lead to complications such as delayed ambulation, restricted ventilation, thromboembolism, and increased duration of hospital stay.¹⁻⁴

Most commonly non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics such as fentanyl and morphine are considered for post-operative pain relief. However, these drugs do not result in complete abolition of pain and often patient develops tolerance toward these drugs.⁵ Most patients with back pain would have received multiple over the counter pain medication, intravenous NSAIDs, tramadol, and they would have already developed tolerance to these pain medications.

Ketamine, a phencyclidine derivative, was introduced in the early 1960s as an anesthetic agent with minimal

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negative effects on the cardiac and respiratory system. Ketamine's analgesic properties are due to reversible antagonism of the N-methyl D-aspartate receptor, opioid receptors, muscarinic receptors, monoaminergic receptors, γ -aminobutyric acid receptors, and several others. At sub-anesthetic doses (≤ 0.3 mg/kg IV), ketamine produces analgesia with minimal effects on consciousness and higher mental functions. Usage of ketamine in sub-anesthetic doses for analgesia has recently increased.⁶⁻¹⁰

The previous studies have used sub-anesthetic ketamine in various dose ranges (0.1–0.3 mg/kg intermittently every 20–30 min or 0.1–0.3 mg/kg bolus dose followed by 1–6 mcg/kg/min infusion intraoperative and in post-operative period) for effective post-operative pain relief.⁶⁻¹⁰ We undertook this study to evaluate the efficacy of sub-anesthetic dose of ketamine using 0.3 mg/kg bolus followed by 4 mcg/kg/min intraoperatively after induction of general anesthesia on post-operative analgesia in patients undergoing single level lumbar discectomy.

Aims and objectives

The primary aim of the study was to determine the effectiveness of intraoperative infusion of sub-anesthetic dose of ketamine on post-operative analgesia in patients undergoing single level lumbar discectomy under general anesthesia in comparison with placebo.

Secondary objectives were to determine the postoperative opioid sparing effect and side effects if any.

MATERIALS AND METHODS

A prospective, double blinded, randomized, and comparative study was conducted after Institutional Ethical Committee approval (RRMCH-IEC/16/2020-21, 20/06/2020), Clinical trial registry-India (CTRI) registration (CTRI/2020/07/026692, July 20, 2020), and informed written consent of the patients.

Sixty patients of either gender, aged between 18 and 65 years with American society of anesthesiologist's physical status I and II posted for single level lumbar discectomy under general anesthesia, were included in the study. Exclusion criteria included patient with high-risk coronary or vascular diseases, hepatic and renal dysfunction, history of psychosis, elevated intracranial pressure or traumatic brain injury, and uncontrolled hypertension.

Pre-anesthetic evaluation was done and patients were explained about numerical rating scale (NRS) (0=no pain, a score of 1–3 – mild pain, a score of 4–6 – moderate

pain, and a score of 7–10 – severe pain) that was used for pain assessment.

All patients were nil by mouth 6 h before surgery. On arrival to operation theatre, an intravenous line was secured. Pulse oximeter, non-invasive blood pressure cuff (NIBP), and ECG electrodes was applied. Baseline heart rate, NIBP, and SPO₂ were noted. Patients were randomly divided into two groups of 30 each using computer generated random numbers and group allocation was concealed by sealed opaque envelope method. Randomization and preparation of the study drugs were done by principal investigator. Outcome measures were observed by another independent anesthesiologist. Patient and assessor of outcome measures were blinded to group allocation.

Patient was pre-medicated with IV glycopyrrolate 0.2 mg, midazolam 1mg, and pre-oxygenated with 100% of oxygen. Analgesia was provided with fentanyl 2 mcg/kg IV in both the groups, induced with propofol 1–2 mg/kg and muscle relaxation was achieved by vecuronium 0.1 mg/kg IV. Patient was then intubated with a cuffed endotracheal tube of appropriate size and airway was secured. Heart rate, electrocardiography, NIBP, oxygen saturation, and end tidal carbon dioxide measurement was monitored throughout the procedure. After intubation, Group A patients received Ketamine 0.3 mg/kg IV bolus followed by infusion at 4 μ g/kg/min in a 50 mL syringe infusion pump containing 2 mg/mL of Ketamine whereas Group B received 0.9% saline bolus dose of similar volume and infusion was started at similar rate.

In both the groups, anesthesia maintenance was carried out by Isoflurane titrated to 1 MAC along with oxygen and nitrous oxide (50:50 ratio). Muscle relaxation was continued with vecuronium 1mg bolus dose administered intermittently based on clinical assessment for all patients and total number of vecuronium doses administered was noted. At the end of the surgery, Ondansetron 4 mg IV and Dexamethasone 8 mg IV were given for nausea; vomiting prophylaxis and infusion of study drugs were stopped. Inhalational agent was cut off and residual neuromuscular blockade was reversed. Patient was extubated after the extubation criteria was met. In post-operative period, rescue analgesia Tramadol 50 mg slow IV was used when NRS score was ≥ 4 . The duration of analgesia was recorded and number of doses of rescue analgesic was recorded. Postoperatively, patient was monitored for 24 h. Sedation was evaluated using Ramsay sedation score. Adverse effects such as nausea, vomiting, and hallucinations if any were noted and treated.

Sample size estimation¹¹

Based on outcome variables from previous literature for cumulative opioid consumption at 24 h, with a mean

difference of 30%, standard deviation in Group A 5.07 and in Group B 5.2, statistical power of 90% and a level of significance – 0.05, a sample size of 60 with 30 patients in each group was obtained.

Statistical analysis

Data were entered into Microsoft excel data sheet and were analyzed using SPSS 22 version software. Categorical data were represented in the form of frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data were represented as mean and standard deviation. Independent t-test or Mann–Whitney U-test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables, respectively. Graphical representation of data: MS Excel and MS word were used to obtain various types of graphs such as bar diagram, Pie diagram, and Line diagram. P<0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software

MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

RESULTS

Sixty patients undergoing single level lumbar discectomy were recruited and received treatment without any dropouts (Figure 1). The demographic data and duration of surgery were comparable in both the groups (Table 1).

Pain scores (NRS) were analyzed at different intervals of time and there was significant difference in mean NRS score comparison between two groups from 1 h to 6 h. NRS score was significantly lesser in Group A than Group B along with prolonged duration of post-operative analgesia in Group A (Tables 2 and 3).

Post-operative consumption of rescue analgesic tramadol was recorded at different time intervals and there was significantly lower tramadol consumption in ketamine group up to 6 h (Table 4).

Control group was relatively more awake than ketamine group in the immediate 0–1 h (Table 5). Both the groups were hemodynamically stable. However, ketamine group had lower mean arterial pressure than control group (Figures 2 and 3).

There was significant difference in comparison of vecuronium dose (mg) used for maintenance of anesthesia after intubation between the two groups, P≤0.001 (Table 6).

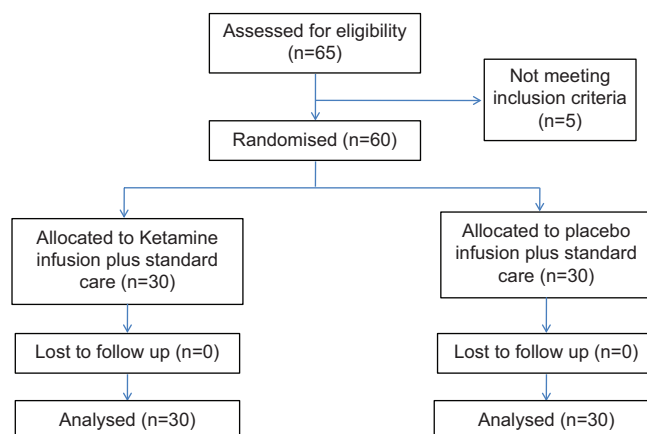


Figure 1: Consort diagram

Table 1: Demographic profile and duration of surgery of two study groups

Parameters	Group A (cases)	Group B (control)
Age in years (Mean±SD)	38.36±12.03	46.43±12.04
Gender (Male/Female)	19/11	13/17
BMI (Mean±SD)	23.82±4.69	23.51±4.09
ASA status I/II	15/15	14/16
Duration of surgery (minutes)	138.2±26.61	137.83±26.49

ASA: American society of anesthesiologists

DISCUSSION

We observed reduced NRS scores in ketamine group compared to control group for initial 8 h which implies that pain relief was better in patients who received intraoperative ketamine infusion compared to control group in initial 8 h. Consumption of tramadol was significantly lower especially between 4 and 8 h in ketamine group compared to control group (Tables 2-4).

Post-operative pain is a type of acute pain due to surgical trauma with an inflammatory reaction and initiation of an afferent neuronal barrage. Effective management of post-operative pain is essential to minimize the dose of medications to lessen side effects and provide adequate analgesia thereby reducing post-operative morbidity rate, delayed recovery, and increased hospital costs.^{12,13}

Ketamine has been used as intravenous induction agent for general anesthesia and analgesia for several decades. Ketamine, at sub-anesthetic doses 0.3 mg/kg bolus dose followed by 1–6 mcg/kg/min infusion, provided effective post-operative pain relief. This may be due to ketamine’s inhibitory effect on both peripheral and central sensitizations at the level of modulation. The pain-prevention mechanisms of ketamine are said to be the inhibition of sensitization of the nociceptive

Table 2: Mean NRS score comparison between two groups at different intervals of time

Time	Group						P-value
	Ketamine (group A)			Control (group B)			
	Mean	Median	SD	Mean	Median	SD	
0 h	0.00	0.00	0.00	0.00	0.00	0.00	
1 h	0.00	0.00	0.00	1.17	1.00	0.83	<0.001*
2 h	1.07	1.00	0.83	2.87	3.00	0.78	<0.001*
4 h	2.07	2.00	0.83	4.47	4.00	0.82	<0.001*
6 h	3.50	3.00	1.66	6.87	7.00	1.46	<0.001*
12 h	7.90	8.00	0.88	7.03	7.00	1.43	0.006*
24 h	6.50	6.00	0.94	6.67	6.00	1.45	0.598

Table 3: NRS score at the time of first rescue analgesic and duration of analgesia

Parameter	Group A	Group B	P-value
Mean NRS score at the time of first rescue analgesic	5.2	6.7	<0.001
Average duration of analgesia (hours)	8.5	4.25	<0.001

pathways, prevention of activation of the nociceptive system associated with opiates, and prevention of opiate tolerance.¹⁴⁻¹⁶ Hence, ketamine 0.3 mg/kg followed by 4 mcg/kg/min infusion was used for postoperative relief in the present study. Patients who benefit most from sub-anesthetic ketamine are those surgeries associated with severe acute post-operative pain such as spine, thoracic, and intra-abdominal surgeries.¹⁷ Patients with spine disorders would have received multiple over the counter pain medication, intravenous NSAIDS, and tramadol, thereby developing tolerance to these pain medications. Hence, we chose patients undergoing lumbar spine discectomy surgery for this study using sub-anesthetic ketamine.

NRS score at the time of first rescue analgesic is significantly lower in Group A when compared to Group B (NRS 5.2 vs. 6.3). Mean duration of analgesia (in hours) shows statistically significant difference between the two groups. (P≤0.001) showing longer duration of analgesia in Group A when compared to Group B (Table 3).

These results were comparable with the study conducted by Hadi et al.,¹⁸ which showed significantly less pain score in ketamine group when compared to remifentanyl group (P<0.05).

Study conducted by Nitta et al.,¹⁹ also showed that there were significantly lower VAS scores in ketamine study group postoperatively at 24, 36, and 48 h. Cumulative morphine consumption was significantly lower in ketamine and ketamine/clonidine study group when compared to control group. No adverse effect was seen

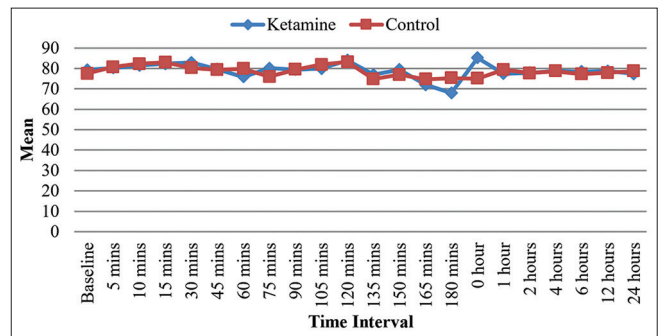


Figure 2: Line diagram showing mean heart rate comparison between two groups at different intervals of time

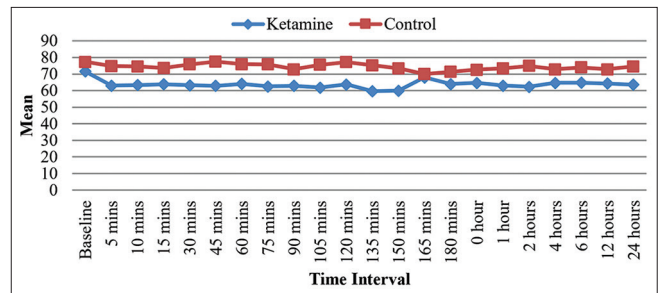


Figure 3: Line diagram showing mean map comparison between two groups at different intervals of time

in either of the groups which were comparable with our study.

The demand for first rescue analgesic at 2nd h postoperatively was nil in Group A, whereas 13.33% of patients in Group B required rescue analgesic, which was not statistically significant in both the groups. The demand for rescue analgesic was significantly less in Group A when compared to Group B at 4th and 6th h (Table 5). This signifies that cumulative opioid consumption in Group A was lower than Group B which is comparable with study conducted by Kim et al.,²⁰ In their study, they compared two different doses of intraoperative ketamine infusion for spine fusion surgeries with patient controlled analgesia using fentanyl, which showed that the total amount of fentanyl consumption was significantly lower in the K2 group (474 µg) compared to the control group (826 µg)

Table 4: Demand for rescue analgesic (Inj. Tramadol 50 mg IV) Distribution between two groups at different intervals of time

Time and demand for rescue analgesic	Group				P-value
	Ketamine (Group A)		Control (Group B)		
	Count	%	Count	%	
0 h					
No	30	100.00	30	100.00	
1 h					
No	30	100.00	30	100.00	
2 h					
No	30	100.00	26	86.67	P=0.05
Yes	0	0.00	4	13.33	
4 h					
No	30	100.00	22	73.33	P=0.002*
Yes	0	0.00	8	26.67	
6 h					
No	23	76.67	0	0.00	P=<0.001*
Yes	7	23.33	30	100.00	
12 h					
Yes	30	100.00	30	100.00	
24 h					
Yes	30	100.00	30	100.00	

Table 5: Sedation (Ramsay) score Distribution between two groups at different intervals of time

Time and sedation score	Group				P-value	
	Ketamine (group A)		Control (group B)			
	Count	%	Count	%		
0 h	2	26	86.67	30	100.00	P=0.038*
	3	4	13.33	0	0.00	
1 h	1	26	86.67	30	100.00	P=0.038*
	2	4	13.33	0	0.00	
2 h	1	30	100.00	30	100.00	
4 h	1	30	100.00	30	100.00	
6 h	1	30	100.00	30	100.00	
12 h	1	30	100.00	30	100.00	
24 h	1	30	100.00	30	100.00	

Table 6: Comparison of number of vecuronium doses used in between the two groups

Groups	Number of vecuronium doses used (Mean±SD)	P-value
Group A	3.03±0.85	<0.001*
Group B	5.04±1.27	

and the K1 group (756 µg) during the 48 h after surgery (P<0.05).

In this study, intraoperative and post-operative mean heart rate was comparable between both the groups. Mean arterial pressure in the intraoperative period was lesser in Group A patients compared to Group B (Figure 3) which was statistically significant. This implies, there was probably hypotensive anesthesia in Group A, providing better field of surgery which was appreciated by the operating surgeon (who was blinded) during the procedure. This could be because of good intraoperative analgesia provided by sub-anesthetic dose of Ketamine infusion. However, we did not

find any similar results regarding hypotensive anesthesia in previous literatures.

There was significant difference in sedation (Modified Ramsay sedation scale) score distribution between two groups from 0 h to 1 h postoperatively (Table 5). Placebo group was relatively more awake than the ketamine group in immediate 0–1 h. However, ketamine group patients were tranquil, cooperative, and responded to oral commands (sedation score 2 and 3). Other complications such as nausea, vomiting, hallucination, and dissociation were not seen in either of the groups which were comparable with studies conducted by Kim et al.,²⁰ and Cengiz et al.,¹¹ which did not show any adverse effects with sub-anesthetic doses of ketamine.

In addition, we observed that there was statistically significant difference in comparison of number of vecuronium doses used between the two groups, P≤0.001 (Table 6). We did not find any mention of this observation in other studies.

Limitations of the study

(1) Duration of follow-up of patient was restricted for only 24 h. Hence, we could not evaluate its long-term effect. (2) Our study population included single level discectomies. Effect on multi-level discectomy and other spine surgeries to be evaluated. (3) Patient controlled analgesia could not be used in the post-operative period due to resource limitation.

CONCLUSION

In lumbar single level discectomy surgeries, intraoperative infusion of sub-anesthetic dose of ketamine provides effective analgesia postoperatively with reduced NRS score, prolonged post-operative analgesia, and decreased opioid consumption with no adverse effects.

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FUTURE SCOPE

Further studies can be conducted to know the effect of sub-anesthetic dose of ketamine infusion on intraoperative blood loss and requirement of anesthetic agents.

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Authors' Contributions:

SMJI- Contributions to conception or design of work, literature review, interpretation of result and preparation of manuscript; **SMR**- Literature review, data collection, statistical analysis and interpretation and preparation of manuscript; **SK**- Analysis and drafting data, interpretation of results, revision of manuscript.

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