

Original Research Article

Intra-operative low-dose ketamine versus dexmedetomidine for attenuation of acute postoperative pain following laparoscopic cholecystectomy: a randomized clinical trial

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ABSTRACT

Background: Ketamine and dexmedetomidine are opioid-sparing agents with distinct analgesic properties. Ketamine is valued for its ability to prevent central sensitization and hyperalgesia without causing respiratory depression. Dexmedetomidine exhibits sedative, anxiolytic, analgesic, anaesthetic, and sympatholytic effects. This study hypothesized that a low-dose combination of ketamine and dexmedetomidine would offer superior analgesia compared to either agent alone when used as an adjuvant during balanced general anaesthesia.

Methods: Sixty patients scheduled for elective laparoscopic cholecystectomy under general anaesthesia were randomized into four groups group D: dexmedetomidine 0.25 µg/kg i.v., group K: ketamine 0.25 mg/kg i.v., group DK: combination of dexmedetomidine and ketamine at the same doses, group S: normal saline. All drugs were diluted to 5 ml and administered intravenously 20 minutes before anticipated skin closure. Postoperative VAS scores and sedation were assessed. The time to first rescue analgesia and total diclofenac consumption over 24 hours were documented.

Results: Postoperatively, group DK demonstrated significantly lower VAS scores at rest and during movement across multiple time points compared to the other groups ($p < 0.05$). The combination group also had the longest time to first rescue analgesia and the lowest total diclofenac requirement. No significant adverse effects were reported in any of the groups.

Conclusions: A low-dose combination of ketamine and dexmedetomidine administered prior to skin closure in laparoscopic cholecystectomy significantly improves postoperative analgesia without increasing side effects. This combination appears to be a safe and effective strategy for enhancing pain control following laparoscopic cholecystectomy.

Keywords: Cholecystectomy, Dexmedetomidine, Ketamine, Post-op analgesia

INTRODUCTION

Post-operative pain control is indispensable for early rehabilitation and shorter hospital stays. However, post-operative pain is still inadequately controlled.¹ Opioid analgesics have been used for post-operative pain control since time immemorial.² However, due to the well-recognized side effects of opioid analgesics like

respiratory depression, nausea, vomiting, ileus, hyperalgesia, and deterioration of consciousness, their use has decreased.³ Moreover, the use of increased doses of opioids in the intraoperative period can cause central sensitization⁴ and allodynia.⁵ Meanwhile, several studies have shown that multimodal analgesia usage can improve patient outcomes regarding post-operative pain.⁶

Both ketamine and dexmedetomidine have been used as adjuvant analgesics to produce the opioid-sparing effect. Ketamine doesn't have respiratory depression, and it also prevents hyperalgesia and central sensitization.⁷⁻⁹ On the other hand, dexmedetomidine is a potent and highly selective α_2 -adreno-receptor agonist, and it has sedative-hypnotic, anxiolytic, analgesic, anaesthetic, and sympatholytic effects.¹⁰

However, few studies have compared ketamine and dexmedetomidine as "intra-operative analgesic adjuvants". In this study, we hypothesized that the combination of low-dose ketamine and dexmedetomidine will be superior to either agent alone when supplemented as an adjuvant analgesic during balanced general anaesthesia. Hence, we aimed to compare the adjuvant analgesic effect of using low-dose ketamine, dexmedetomidine, or a combination of the two with a placebo group.

METHODS

This study was a randomized, double-blinded, controlled clinical trial conducted over a two-year period (May 2022 to June 2024) at a tertiary care hospital in Manipur, India. Ethical clearance was sought from the Institutional Ethics Committee (Research Ethics Board RIMS), and the trial was registered with the Clinical Trials Registry of India (CTRI/2023/10/059009).

Male and female patients within the age group of 18 to 60 years, belonging to ASA physical status I or II, who were posted for elective laparoscopic cholecystectomy under general anaesthesia, were included in the study after obtaining written informed consent.

Patients with substantial cardiovascular disease (e.g., myocardial infarction within the past 6 months) or those whose surgeries were converted to open procedures were excluded from the study.

The sample size was calculated by comparing with a study by Garg et al, which reported postoperative 24-hour morphine consumption as 6.89 ± 5.88 mg (dexmedetomidine group) and 2.45 ± 2.06 mg (ketamine group).¹⁷ Using a significance level of $\alpha=0.05$ and a power of 80%, the required sample size was 13 patients in each group. Considering a 5% dropout rate, the final sample size was set at 15 patients per group, totalling 60 patients across four groups.

Group allocation

Group D: injection dexmedetomidine 0.25 μ g/kg, Group K: injection ketamine 0.25 mg/kg, group DK: combination of dexmedetomidine 0.25 μ g/kg and ketamine 0.25 mg/kg, group S: 5 ml normal saline (placebo).

All drugs were diluted to a 5 ml volume and administered as a slow i.v. injection 20 minutes before anticipated skin closure.

Both the patient and the primary investigator were blinded to group assignments. The study drugs were prepared and randomized by an independent anaesthesiologist who was not involved in the study.

Anesthetic technique and intraoperative management

All patients underwent pre-anaesthetic evaluation a day before surgery and were advised oral alprazolam 0.5 mg at bedtime. In the pre-anaesthetic room, Intravenous access was secured in the right hand with an 18-G cannula for fluid administration.

On arrival at the operating theatre, standard baseline monitoring (HR, NIBP, SpO₂, ECG) was initiated. Induction of general anaesthesia was achieved with propofol 1.5-2 mg/kg i.v. over 60 seconds and fentanyl 2 μ g/kg i.v., followed by cis-atracurium 0.2mg/kg i.v. for neuromuscular blockade. Patients were ventilated with 100% oxygen for 2-3 minutes to facilitate endotracheal intubation.

After intubation, end-tidal CO₂ (ETCO₂) and temperature monitoring were commenced. ETCO₂ was maintained between 30-35 mmHg, and normothermia was maintained. Anaesthesia was maintained using O₂:N₂O (40:60) at 1.5 l/minute and sevoflurane (0.6-2%), titrated to maintain a BIS value of 40-60 and MAC of 0.5-1.0. cis-atracurium top-ups ($\frac{1}{4}$ of the initial dose) were given as required.

Intraoperative hemodynamic parameters were recorded every 5 minutes for the first 30 minutes, then every 15 minutes till the end of the surgery. Bradycardia (HR<50/minute) was countered with atropine 0.3 mg i.v. in increments; tachycardia (HR>110/minute) with esmolol 10 mg i.v. in increments.

Study drugs were administered 20 minutes prior to skin closure, as per group allocation. Diclofenac 75 mg i.m./i.v. was given concurrently as part of multimodal analgesia. Antiemetic prophylaxis consisted of ondansetron 0.2 mg/kg i.v. and dexamethasone 0.2 mg/kg i.v., administered 10 minutes prior to the end of surgery.

Anaesthetic gases were discontinued 5-10 minutes before reversal. Neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrrolate 0.008 mg/kg i.v. Extubation was performed once spontaneous ventilation and verbal responsiveness were confirmed. Patients were then shifted to the post-anaesthesia care unit (PACU) for monitoring.

Patients were then assessed for sedation and pain in the post-anaesthesia care unit (PACU) using the Ramsay sedation score (RSS) and the visual analogue scale (VAS), respectively, at 30 minutes, 1 hour, and 2 hours

postoperatively. Subsequent assessments were conducted at 6, 12, and 24 hours in the ward.

The time to first rescue analgesia was defined as the interval from arrival in the PACU to the first instance of a VAS score of 4 or greater. Rescue analgesia was administered as injection diclofenac (aqueous) 75 mg i.m. or i.v., depending on clinical judgment. The total dose of rescue analgesic administered within the first 24 hours postoperatively was recorded.

Postoperative nausea and/or vomiting (PONV) occurring within the first 6 hours postoperatively was also documented.

All data were recorded on a pre-designed proforma and reviewed for completeness and accuracy. Measures were

taken to ensure confidentiality, and all records were securely stored.

Data analysis was conducted using SPSS version 26.0 for Windows. Categorical variables (e.g., sex, ASA status) were analyzed using the Chi-square test, while analysis of variance (ANOVA) was used for parametric data, and the Kruskal-Wallis test for non-parametric data. Post hoc pairwise comparisons were performed using the Bonferroni correction where appropriate. A p value <0.05 was considered statistically significant.

RESULTS

The demographic parameters such as age, gender, weight, and height of the patients were comparable in all four groups as shown in Table 1.

Table 1: Demographic profile of the study participants (n=60).

Parametes	Control group (n=15)	Dexmedetomidine group (n=15)	Dexmed-Keta group (n=15)	Ketamine group (n=15)	P value
Age (in years)	42±10.76	38.93±14.71	34.13±9.6	43.80±10.71	0.102
Gender	Female	11 (26.8%)	12 (29.3%)	9 (22%)	0.556
	Male	6 (31%)	4 (21.1%)	6 (31.6%)	
Weight (in kg)	67.50±8.82	62.87±10.99	62.27±12.37	65.33±8.67	0.493
ASA	I	12 (24.5%)	11 (22.4%)	14 (28.6%)	0.549
	II	3 (27.3%)	4 (36.4%)	1 (9.1%)	

Table 2: VASR (VAS score at rest) at different time intervals among the four groups.

		Sum of squares	F value	P value
VAS_R 0 hour	Between-group	20.93	10.28	0.000
	Within group	38.00		
VAS_R 1 hour	Between-group	34.98	10.48	0.000
	Within group	62.27		
VAS_R 2 hours	Between-group	11.17	8.84	0.000
	Within group	23.46		
VAS_R 6 hours	Between-group	22.53	5.59	0.002
	Within group	75.20		
VAS_R 12 hours	Between-group	2.73	0.77	0.51
	Within group	65.60		
VAS_R 24 hours	Between-group	2.20	1.44	0.23
	Within group	28.40		

The total duration of surgery and anaesthesia among the four groups was found to be statistically insignificant (p values 0.642 and 0.548, respectively).

Ramsay sedation scores (RSS) at different time intervals in post-op among the four groups were comparable and not statistically significant (p>0.05).

Post-hoc analysis of VASR in the four groups revealed that VASR at 0 hours, 1 hour, and 2 hours was higher in the Control group than in the other groups.

Post-hoc analysis of VASR in the four groups found that VASR at 6 hours was higher in the control group as compared to the Dexmed-Keta group.

Post-hoc analysis of VASM in the four groups showed that VASM at 0 hours, 1 hour, and 2 hours was higher in the Control group than in the other groups.

Post-hoc analysis of VASM in the four groups found that VASM at 6 hours was higher in the control group as compared to the Dexmed-Keta group.

Table 3: VASM (VAS score at movement) at different time intervals among the four groups.

		Sum of squares	F value	P value
VAS _M 0 hour	Between-group	39.36	8.79	0.000
	Within group	83.33		
VAS _M 1 hour	Between-group	32.85	10.08	0.000
	Within group	60.80		
VAS _M 2 hours	Between-group	6.98	6.51	0.001
	Within group	20.00		
VAS _M 6 hours	Between-group	25.51	4.55	0.006
	Within group	104.67		
VAS _M 12 hours	Between-group	4.13	1.03	0.38
	Within group	74.80		
VAS _M 24 hours	Between-group	1.13	0.379	0.76
	Within group	55.86		

Table 4: Time of first rescue analgesic (in minutes).

Time of first rescue analgesic	Control	Dexmedetomidine	Dexmed-Keta	Ketamine	P value
Mean ±SD	85.38±87.33	330.00±171.46	600±207.84	272±115.10	0.000

Table 5: The total dose of rescue analgesic given in the first 24 hours post-op (in mg).

Total dose of rescue analgesic	Control	Dexmedetomidine	Dexmed-Keta	Ketamine	P value
Mean±SD	115.00±62.53	70.00±34.33	10.00±26.38	45.00±47.43	<0.002

The time of the first rescue analgesic is the total time taken by the patient to reach a VAS score of 4 or higher when they ask for an analgesic. In other words, it is the total duration of analgesia. Of the four groups, the Dexmed-Keta group experienced the longest post-operative analgesia, whereas the control group had the shortest. The mean time to the first rescue analgesic was compared, and the difference was statistically significant with a p value of 0.000. Post hoc analysis was performed using the Bonferroni test, which revealed that the mean total duration of analgesia in the control group was significantly less than in the other three groups. Additionally, the mean total duration of analgesia in the dexmedetomidine-ketamine group was significantly longer than in the dexmedetomidine and ketamine groups.

Among the four groups, the Dexmed-Keta group had the least dose of rescue analgesic in the first 24-hour post-op period compared to the other three groups and the control group received the maximum dose of rescue analgesic. The mean total dose of rescue analgesic administered in the first 24 hours post-operatively among the four groups was found to be statistically significant, with a p value of 0.000 using the one-way ANOVA test.

Post-hoc analysis of the total analgesic dose administered in the four groups revealed that the mean total rescue analgesic dose given in the first 24 hours post-operatively in the control group was greater than that in the other three groups. Also, the mean total rescue analgesic dose given

in the first 24 hours post-op in the dexmedetomidine group was more than the Dexmed-Keta group.

DISCUSSION

In this study, the Dexmed-Keta group required the least rescue analgesic (injection diclofenac i.m.) in the first 24 hours postoperatively (10±26.38 mg), followed by the ketamine group (45±47.43 mg), the dexmedetomidine group (70±34.33 mg), and the control group, which required the highest dose (115±62.53 mg). These findings align with the study by Mitra et al, who compared low-dose ketamine and dexmedetomidine in lumbar spine surgeries.¹¹ They found significantly higher PCA-fentanyl use in the saline group as compared to the ketamine and dexmedetomidine groups, though both drugs showed comparable analgesic effects.

Garg et al similarly reported that patients receiving low-dose ketamine and dexmedetomidine infusions during spine surgery had significantly reduced morphine requirements at 24 and 48 hours post-op compared to controls.¹⁷ Gupta et al found that postoperative mechanically ventilated patients who received only dexmedetomidine had higher pain scores at 2 and 4 hours post-op compared to those who received both dexmedetomidine and ketamine (p<0.05).¹⁹

In a study by Thappa et al, patients undergoing spine surgery who received fentanyl required more rescue analgesics and had higher postoperative pain scores

compared to those given a low-dose ketodex infusion ($p=0.03$).²² Gurbet et al also found higher cumulative morphine consumption in patients receiving dexmedetomidine infusion following total abdominal hysterectomy, compared to those given a placebo infusion in the post-anesthesia care unit ($p<0.05$) and in the ward ($p<0.01$).²⁵

Similarly, Mercanoğlu et al reported significantly higher PCA-morphine use in patients undergoing laparoscopic cholecystectomy under TIVA (with remifentanyl, propofol, and rocuronium) who did not receive ketamine or dexmedetomidine.²⁴ The addition of either agent significantly reduced morphine consumption ($p<0.001$ for both).

In this study, the Dexmed-Keta group demonstrated the longest time to first rescue analgesic (600 minutes), followed by group dexmedetomidine (330 minutes), group ketamine (272 minutes), and the control group, which had the shortest duration (85 minutes). These differences were statistically significant ($p=0.000$). The total duration of analgesia was also significantly longer in the Dexmed-Keta group compared to both the dexmedetomidine and ketamine groups. However, the dexmedetomidine and ketamine groups had comparable durations of analgesia, which was not statistically significant ($p>0.005$).

These findings are similar to a study by Karasu et al who reported significantly shorter time to rescue analgesia in patients receiving TAP block with bupivacaine alone after laparoscopic cholecystectomy, compared to those who received bupivacaine with dexmedetomidine or ketamine ($p<0.001$).¹³ Similarly, Mohamed et al found a significantly longer time to first rescue analgesic in patients receiving a brachial plexus block with bupivacaine and dexmedetomidine for upper limb surgeries, compared to those receiving bupivacaine with ketamine or bupivacaine alone ($p<0.0001$).¹⁶

In another study by Thappa et al, a combination of low-dose ketamine and dexmedetomidine infusion provided a significantly longer time to first rescue analgesia in spine surgery patients than fentanyl infusion alone ($p<0.001$).²² Likewise, Malek et al found that patients undergoing laparoscopic cholecystectomy who received an i.m. combination of dexmedetomidine, ketamine, fentanyl, and atropine had a significantly longer time to first rescue analgesia compared to those who received combinations with alfentanil ($p<0.01$) or pethidine ($p<0.05$).²⁶

In this study, the Dexmed-Keta group had significantly lower VAS scores at rest and on movement when compared to the other three groups at 0, 1, and 2 hours postoperatively. This indicates that the combination of dexmedetomidine and ketamine provides a superior quality of analgesia compared to either drug used alone.

These findings are supported by previous studies. El Badawy et al reported that intra-articular bupivacaine

combined with dexmedetomidine resulted in lower VAS scores than bupivacaine with ketamine, and both combinations were more effective than bupivacaine alone in patients undergoing knee arthroscopy.¹² Similarly, Karasu et al found significantly lower VAS scores at 0 and 2 hours post-op in patients receiving a TAP block with bupivacaine and dexmedetomidine, compared to those receiving bupivacaine with ketamine or bupivacaine alone.¹³

Gupta et al also observed that pain scores were significantly lower in ICU patients receiving a combination of dexmedetomidine and ketamine infusions following major abdominal or head and neck surgeries, compared to those receiving dexmedetomidine alone, at 2 and 4 hours post-extubation.¹⁹ Additionally, sedation scores were significantly higher in the combination group at 2 hours.

In our study, the dexmedetomidine and ketamine group had comparable VAS at rest and on movement at 0 hour, 1 hour, 2 hours, 6 hours, 12 hours, and 24 hours postoperatively. This is consistent with the findings of Mitra et al, who reported similar analgesic efficacy between low-dose ketamine and dexmedetomidine infusions in patients undergoing elective lumbar spine surgeries.¹¹

Furthermore, Garg et al observed that patients receiving combined low-dose ketamine and dexmedetomidine infusions during spine surgery experienced sedation, though none required airway intervention.¹⁷ In contrast, none of our patients experienced delayed recovery, excessive drowsiness, sedation, or hallucinations during the 24-hour postoperative period. This may be attributed to our protocol using a single bolus of low-dose dexmedetomidine ($0.25 \mu\text{g}/\text{kg}$) and ketamine ($0.25 \text{mg}/\text{kg}$) rather than a continuous infusion.

CONCLUSION

A low-dose combination of ketamine and dexmedetomidine administered prior to skin closure in laparoscopic cholecystectomy significantly improves postoperative analgesia without increasing side effects. This combination appears to be a safe and effective strategy for enhancing pain control following laparoscopic cholecystectomy.

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