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Original Research Article

Ketamine-Dexmedetomidine Analgesia in Laparoscopic Cholecystectomy

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Abstract:

Background: Even though laparoscopic cholecystectomy is a common day-care treatment, postoperative discomfort is still a major problem that causes recovery and release to be delayed. The best approach to lessen this discomfort and cut back on opiate use is multimodal analgesia.

Objective: This study's main goal was to assess the analgesic effectiveness of Ketamine plus Dexmedetomidine (Ketodex) versus Ketamine alone in individuals having elective laparoscopic cholecystectomy. Assessing the incidence of side effects, total analgesic intake, and the time to first rescue analgesia were secondary goals.

Methods: Over the course of eighteen months, a prospective, randomized, double-blind, controlled trial was carried out at the Indira Gandhi Institute of Medical Sciences (IGIMS), Patna. There were 102 patients in all (ASA I & II, ages 18–60). Patients were divided into two groups at random: Group KD got an intravenous bolus of 0.5 mg/kg of ketamine and 0.5 µg/kg of dexmedetomidine, while Group K received 0.5 mg/kg of ketamine alone, given 10 minutes before the incision. Visual Analog Scale (VAS) scores were used to measure postoperative discomfort at 24 hours.

Results: At every postoperative interval, Group KD's VAS scores were considerably lower than Group K's ($p < 0.0001$). Group KD had a considerably longer mean time to first rescue analgesia (10.54 ± 1.98 hours) than Group K (6.21 ± 2.50 hours, $p < 0.0001$). Group KD consumed considerably less rescue analgesics overall (117.64 ± 38.50 mg) than Group K (162.74 ± 48.82 mg). On the other hand, the KD group experienced more nausea and vomiting (19.60%) than the K group (3.92%).

Conclusion: Although it is linked to an increased risk of postoperative nausea, the combination of ketamine and dexmedetomidine offers better postoperative analgesia and a notable opioid-sparing benefit when compared to ketamine alone.

Introduction

One of the most common surgical procedures performed worldwide is laparoscopic cholecystectomy (LC), which is considered the gold standard for treating symptomatic cholelithiasis [1]. Because of its many advantages, it has supplanted open surgery since the National Institutes of Health approved it in the early 1990s [2].

Although the laparoscopic method has several benefits, such as fewer incisions, less tissue damage, and shorter hospital stays, postoperative pain is still a possibility [3]. After LC, the pain is complicated and multifaceted, resulting from a combination of somatic pain from the incision sites, referred shoulder pain from diaphragmatic irritation from the residual carbon dioxide pneumoperitoneum, and visceral discomfort from the gallbladder removal [4].

The Need for Multimodal Analgesia

This severe surgical discomfort might seriously hinder healing if left untreated. In order to preserve pulmonary function and maintain a positive myocardial oxygen balance, patients must be able to breathe deeply and cough properly, which is made possible by adequate pain management. Prolonged hospital stays and higher medical expenses can result from inadequate analgesia. Opioids have always been the mainstay of postoperative pain treatment. Nevertheless, their use is linked to dose-dependent side effects such drowsiness, nausea, vomiting, respiratory depression, and possible addiction. As a result, multimodal analgesia the concurrent use of non-opioid drugs with various mechanisms of action to improve pain management while reducing the need for opioids is emphasized in contemporary anesthesia protocols [5].

Rationale for the Study

Ketamine and dexmedetomidine are two pharmaceuticals that have demonstrated potential as adjuvants in multimodal regimens. Due to its analgesic qualities at sub-anesthetic dosages, the well-known anesthetic ketamine hydrochloride has experienced a comeback in clinical practice [6]. In order to prevent central sensitization and lower postoperative opioid intake, it mainly acts as a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors [7].

In contrast, dexmedetomidine is a very selective α_2-adrenoreceptor agonist that is renowned for its exceptional capacity to produce analgesia, drowsiness, and anxiolysis without seriously impairing breathing [8]. Often called "Ketodex," the combination of these two medicines has potential benefits [9]. Their hemodynamic characteristics complement each other: ketamine may counteract the bradycardia and hypotension linked to dexmedetomidine, while dexmedetomidine can lessen the tachycardia and hypertension frequently caused by ketamine. There is a dearth of research that precisely assesses the analgesic effectiveness of the Ketamine-Dexmedetomidine combination against Ketamine alone in the particular setting of laparoscopic cholecystectomy, despite studies comparing Ketamine with other drugs.

Review of Literature

Evolution of Laparoscopic Cholecystectomy and Pain Management

The introduction of laparoscopic cholecystectomy significantly altered the surgical landscape for gallbladder disease. Patient desire for a technique that promised less postoperative discomfort, shorter hospital stays, and a quicker return to regular daily activities in contrast to the week-long recuperation associated with open cholecystectomy was a major factor in this transition [10, 11]. This should ideally enable "real" outpatient treatments, in which patients are released the same day [12]. To maximize results, however, the timing of the procedure is still crucial, especially in situations of severe pancreatitis [13]. Additionally, although though the surgery is generally safe, major management expenses [14] and long-term morbidity [15] may result from complications including bile duct damage. Notwithstanding these benefits, the process created new difficulties in managing pain, particularly the shoulder and visceral discomfort brought on by peritoneal stretching. In order to lessen these

problems, experts have recommended that a multimodal analgesia approach be used to manage pain after laparoscopic surgery [16].

Ketamine: Pharmacology and Clinical Utility

A phencyclidine derivative, ketamine has a lengthy and diverse medical history. When it was first released in 1970, it was prized for its capacity to create a "dissociative" condition. Its use has undergone a resurgence in recent years, especially at low doses for critical care and acute pain treatment [17]. Ketamine suppresses the "wind-up" phenomena in the spinal cord's dorsal horn by inhibiting the NMDA receptor. It has been demonstrated that preemptive ketamine injection works well during laparoscopic surgeries [18]. Additionally, research contrasting ketamine with other medications such as propofol and remifentanil has demonstrated its effectiveness in lowering the need for postoperative analgesics [19]. The effectiveness of intravenous ketamine for analgesia in this patient population was further validated by a meta-analysis by Ye et al. [20], a conclusion reinforced by Cochrane reviews that highlight its opioid-sparing effects [21].

Dexmedetomidine: Mechanism and Benefits

The growth of dexmedetomidine has coincided with the resurgence of ketamine. This imidazole derivative is a strong α_2-adrenergic agonist that was first approved by the FDA in 1999 for ICU sedation. Dexmedetomidine, in contrast to conventional sedatives, produces a state of drowsiness that closely resembles sleep by acting on the locus coeruleus. Its effectiveness has been proven in a number of surgical specialties. It has been effectively employed, for example, as an anesthetic adjuvant during brain tumor surgery [22]. Compared to remifentanil, it dramatically decreased opioid use during gynecologic videolaparoscopic surgery [23]. Similarly, dexmedetomidine infusions offered better analgesia during airway procedures such uvulopalatopharyngoplasty [24].

The Synergistic Potential of Ketodex

In order to monitor and adjust depth of anesthesia, the idea of combining pharmaceutical drugs to achieve balanced anesthesia (TIVA) has attracted a lot of scholarly interest [25]. The reasoning is based on physiological balance: the sympatholytic effects of dexmedetomidine (bradycardia, hypotension) may be buffered by the sympathomimetic effects of ketamine (tachycardia, hypertension). Similar synergies have been investigated in a number of research. For example, Nitta et al. showed that intravenous low-dose ketamine combined with oral clonidine, another α_2-agonist, decreased morphine consumption after spine surgery [26]. By separating the additive effect of dexmedetomidine when mixed with ketamine, the current work aims to expand on this fundamental understanding.

Materials and Methods

Study Design and Participant Selection

After trial registration and Institutional Ethical Committee permission, this prospective, randomized, double-blind, controlled investigation was carried out over an 18-month period at the Indira Gandhi Institute of Medical Sciences, Patna. 102 adult patients between the ages of 18 and 60 who were scheduled for elective laparoscopic cholecystectomy and had a physical status of I or II according to the American Society of Anesthesiologists (ASA) were included in the study. Individuals having a history of cardiac problems, kidney failure, liver failure, or allergies to the research medicines were excluded, as were patients who declined to participate and those with ASA class III or higher.

Randomization and Blinding Protocols

A minimum of 51 patients were needed for each arm, according to the sample size calculation based on prior research, assuming a 95% power and 95% confidence interval [9]. A computer-generated block randomization technique was used to accomplish randomness. To guarantee allocation concealment, the sequence was created by an impartial statistician and then hidden in opaque envelopes with sequential numbers. An independent anesthesiologist who was not engaged in patient care or data collection prepared the study medications in identical 10 mL syringes in order to preserve the trial's double-blind design. As a result, the study's group allocation was kept a secret from the patients, the anesthesiologists who administered the anesthesia, and the outcome assessors.

Anesthetic Management and Drug Administration

Standard monitoring, including non-invasive blood pressure (NIBP), peripheral oxygen saturation (SpO_2), heart rate (HR), and electrocardiography (ECG), was set up upon arrival in the surgery room. Following three minutes of pre-oxygenation, fentanyl (2 µg/kg), propofol (2 mg/kg), and vecuronium (0.1 mg/kg) were used to induce general anesthesia. Before the skin incision, patients were given the study medication intravenously for ten minutes after successful intubation. Patients in Group KD were given a combination of 0.5 mg/kg of ketamine and 0.5 µg/kg of dexmedetomidine, whereas patients in Group K were given 0.5 mg/kg of ketamine alone, both diluted to a volume of 10 mL with normal saline. Isoflurane $(0.8-1\%)$ in a 1:1 oxygen and nitrous oxide combination was used to maintain anesthesia, with sporadic doses of Vecuronium administered as needed.

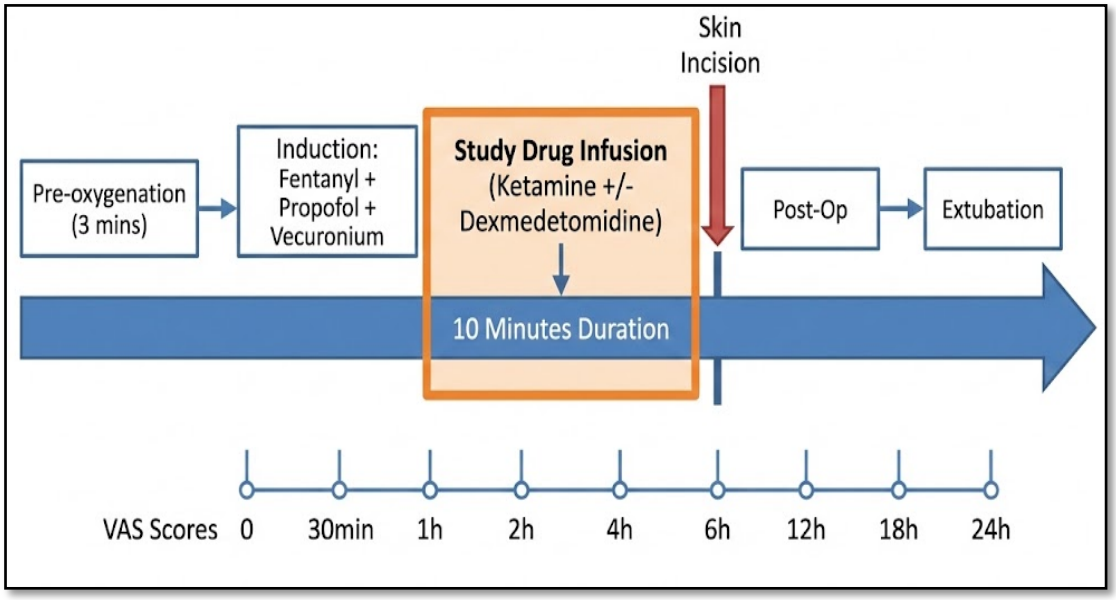

Figure 1 Timeline of anesthetic protocol and postoperative VAS pain score collection

Postoperative Assessment and Outcome Measures

Neostigmine and glycopyrrolate were used to reverse neuromuscular blockade at the end of the procedure, and patients were extubated as soon as their airway reflexes recovered. In the Post-Anesthesia Care Unit (PACU), postoperative evaluation was carried out. The Visual Analog Scale (VAS) was used to measure postoperative pain at the following intervals: 0, 30 minutes, 1, 2, 4, 6, 8, 12, and 24 hours. The time to first rescue analgesia and the total amount of rescue analgesia needed were secondary outcomes. If the VAS score was

higher than 4, rescue analgesia in the form of 100 mg of tramadol was given.

Statistical Analysis

SPSS v23 was used for statistical analysis. For both continuous (mean/SD) and categorical (frequencies) variables, descriptive statistics were employed. The independent sample t-test was used to compare groups for continuous data, and the Chi-square test or Fisher's exact test was utilized for categorical data. Statistical significance was defined as a p-value of less than 0.05.

Results

Demographic and Operative Characteristics

A total of 102 patients were successfully enrolled in the trial, with 51 individuals in the Ketamine-Dexmedetomidine (KD) group and 51 in the Ketamine-only (K) group. The groups were well-matched, according to the study population's demographic profile. Group KD's mean age was 41.45 ± 14.10 years, while Group K's was 45.76 ± 10.46 years. This difference was not statistically significant ($p = 0.0826$). The distribution of sex was also similar, with females making up 70.59% of Group K and 56.86% of Group KD ($p = 0.1513$). The length of the procedure, in particular, did not differ significantly between the two groups (67.64 ± 25.34 min vs. 75.29 ± 30.81 min; $p = 0.1700$), indicating that surgical time did not affect the outcomes.

Table 1 Demographic and Operative Characteristics

Parameter	Group KD (n=51)	Group K (n=51)	p-value
Age (Years) (Mean $\pm$ SD)	41.45 ± 14.10	45.76 ± 10.46	0.0826
Sex (Female/Male) (n)	29 / 22	36 / 15	0.1513
Duration of Surgery (min) (Mean $\pm$ SD)	67.64 ± 25.34	75.29 ± 30.81	0.1700

Intraoperative Hemodynamic Profile

Different pharmacological effects related to the study medications were identified by intraoperative hemodynamic monitoring. Although the groups' baseline heart rates and mean artery pressure (MAP) were comparable, notable alterations emerged soon after the medication was administered. After 15 minutes, Group KD's heart rate was considerably lower than Group K's (77.27 ± 17.14 bpm vs. 86 ± 17.57 bpm; $p = 0.0126$). At 15 minutes, Group KD's mean arterial pressure was lower (86.27 ± 13.16 mmHg) than Group K's (92.65 ± 13.90 mmHg ; $p = 0.0192$). This pattern was similar. These results are consistent with earlier studies by Siddiqui et al. [27], who reported the hemodynamic stabilizing effects of dexmedetomidine in TIVA, and Patel et al. [28], who found comparable recovery benefits using entropy analysis. It's interesting to note that this pattern changed later in the process; after 75 minutes, Group KD had noticeably higher MAP than Group K, indicating either compensatory stabilization or a biphasic hemodynamic response.

Table 2: Intraoperative Hemodynamic Parameters at Key Intervals

Time Interval	Parameter	Group KD (Mean $\pm$ SD)	Group K (Mean $\pm$ SD)	p-value
Baseline	Heart Rate (bpm)	80.41 ± 18.62	85.95 ± 18.57	0.1356
	MAP (mmHg)	93.45 ± 13.91	98.28 ± 17.35	0.1240
15 Minutes	Heart Rate (bpm)	77.27 ± 17.14	86.00 ± 17.57	$\mathbf{0.0126}*$

	MAP (mmHg)	86.27 ± 13.16	92.65 ± 13.90	**0.0192** *
75 Minutes	Heart Rate (bpm)	91.00 ± 16.69	86.00 ± 14.86	0.1132
	MAP (mmHg)	94.45 ± 17.06	88.07 ± 13.18	**0.0371** *

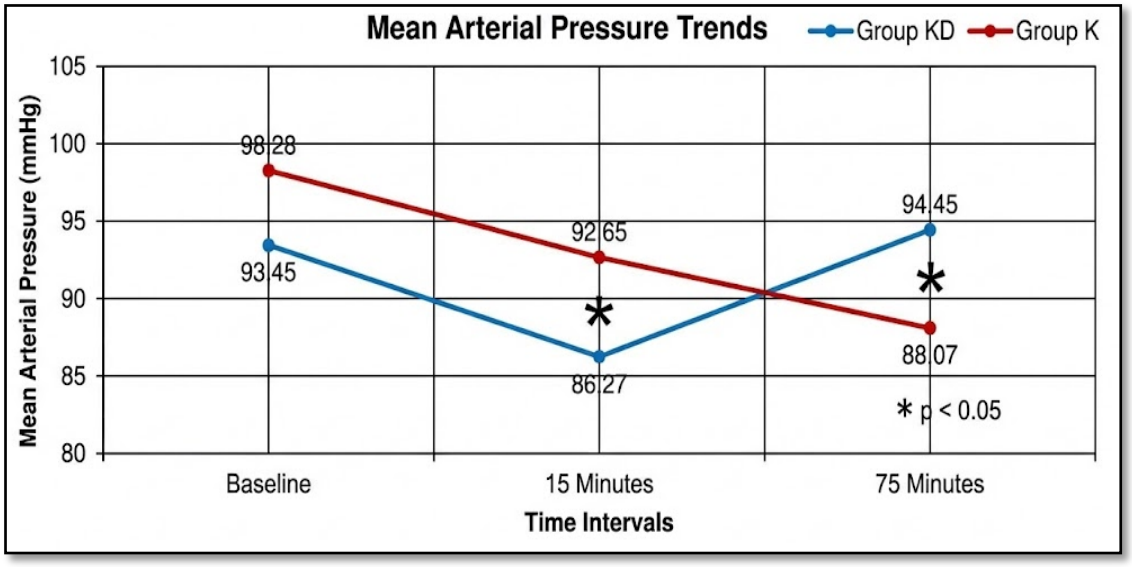

Figure 2 Intraoperative MAP trends showing significant hemodynamic modulation in Group KD compared to Group K at 15 and 75 minutes

Primary Outcome: Postoperative Pain Assessment

The combination therapy was clearly superior in the primary outcome of postoperative pain. At every surgical time point evaluated up to 12 hours, patients in Group KD reported considerably reduced VAS scores. For instance, at 30 minutes, Group KD's mean VAS score was 1.05 ± 0.31, but Group K's was 1.68 ± 0.81 ($p < 0.0001$). Six hours later, Group KD reported a mean score of 3.68, while Group K reported a mean score of 5.87. Both groups reported a VAS of 0 after 24 hours.

Secondary Outcomes: Rescue Analgesia and Adverse Events

Reduced opioid use was a direct result of this improved pain management. In comparison to the K group (6.21 ± 2.50 hours), the KD group's time to first rescue analgesia was almost twice as long (10.54 ± 1.98 hours). Additionally, Group KD consumed considerably less Tramadol overall during the first 24 hours (117.64 ± 38.50 mg) than Group K (162.74 ± 48.82 mg). The frequency of adverse events differed among the groups in terms of safety. Ten patients (19.60%) in Group KD had nausea and vomiting, compared to just five patients (3.92%) in Group K ($p = 0.0144$). Additionally, Group KD experienced bradycardia more frequently (15.7%) than Group K (9.8%), although this difference was not statistically significant ($p = 0.3741$).

Table 2 Postoperative Analgesic Outcomes

Outcome Measure	Group KD (Mean ± SD)	Group K (Mean ± SD)	p-value
VAS Score at 30 min	1.05 ± 0.31	1.68 ± 0.81	**< 0.0001** *
VAS Score at 6 hours	3.68 ± 0.50	5.87 ± 2.94	**< 0.0001** *
VAS Score at 12 hours	5.00 ± 2.52	6.50 ± 1.84	**< 0.0001** *
Time to 1st Rescue Analgesia (hrs)	10.54 ± 1.98	6.21 ± 2.50	**< 0.0001** *

Total Rescue Analgesia (mg)	117.64 ± 38.50	162.74 ± 48.82	$< \mathbf{0.0001} *$

Discussion

This study's main goal was to determine if patients having laparoscopic cholecystectomy would benefit more from the addition of dexmedetomidine to ketamine than from ketamine alone. The outcomes clearly demonstrate the combination's effectiveness (Ketodex).

Interpretation of Analgesic Efficacy

This study's main conclusion is that the Ketodex group's VAS scores significantly decreased at all postoperative time points up to 12 hours. This lends credence to the theory that the two medications work in concert. While dexmedetomidine produces analgesia through α_2-adrenoceptor agonism at the spinal and supraspinal levels, ketamine inhibits NMDA receptors, limiting central sensitization to pain. The results are consistent with earlier research showing enhanced analgesia in other surgical settings using comparable combinations. Clinically, the KD group's pain-free interval was extended to more than ten hours, which may improve the quality of their sleep the night before surgery.

Opioid-Sparing Effects

The "Opioid Crisis" has made it necessary to use less opioids during surgery. In this trial, the Ketodex group needed an average of 45 mg less Tramadol than the control group. The results of Ye et al. [20] on ketamine and Bulow et al. [23] on dexmedetomidine are in line with this opioid-sparing effect. Although the combination therapy introduced its own side effect profile in our sample, it may reduce the incidence of opioid-related respiratory depression by reducing reliance on opioids.

Hemodynamic Modulation

Due to its sympatholytic actions, dexmedetomidine frequently results in bradycardia and hypotension. At 15 and 30 minutes after induction, we noticed this considerably. However, the sympathomimetic counter-effect of ketamine probably prevented the expected severe hemodynamic instability from occurring. This validates the pharmacological justification provided by Siddiqui et al. [27] for combining these two medicines in order to preserve hemodynamic neutrality. An intriguing occurrence that could indicate a compensating mechanism or the wearing off of the dexmedetomidine effect in comparison to ketamine is the late-phase increase in HR and MAP in the KD group at 105 minutes.

Adverse Effects Profile

The safety profile showed significant trade-offs, especially with relation to postoperative nausea and vomiting (PONV), despite the clear analgesic benefits of the Ketodex combination. The Ketamine-Dexmedetomidine group had nausea and vomiting at a considerably higher rate (19.60%) than the Ketamine-only group (3.92%). This discovery is rather different because dexmedetomidine is frequently mentioned as having an opioid-sparing action that should potentially lessen PONV, yet ketamine is known to be emetogenic. However, the greater occurrence in our study might be due to the prolonged sedation that dexmedetomidine causes or to the particular effects it has on the central nervous system when combined with ketamine.

In terms of cardiovascular consequences, bradycardia was more prevalent in the KD group (15.7%) than in the K group (9.8%), which is consistent with dexmedetomidine's recognized sympatholytic effects. Crucially, this difference was not statistically significant, indicating that ketamine's sympathomimetic effects contributed to hemodynamic stability.

Conclusion

The use of Ketamine-Dexmedetomidine (Ketodex) as a useful part of multimodal analgesia in elective laparoscopic cholecystectomy is strongly supported by this prospective, randomized, double-blind controlled trial. When compared to ketamine alone, the combined therapy showed better analgesic efficacy, as evidenced by consistently reduced VAS pain levels at all postoperative time points. The time to initial rescue analgesia was notably extended to 10.54 hours when Ketodex was administered, as opposed to just 6.21 hours in the Ketamine-only group. The Ketodex group required substantially less total rescue tramadol (117.64 mg) during the first 24 hours compared to the control group (162.74 mg), indicating a strong opioid-sparing effect. The addition of dexmedetomidine was linked to a statistically significant increase in the incidence of nausea and vomiting (19.6%) as compared to the control group, even though hemodynamic stability was mainly preserved. Therefore, even though Ketodex successfully improves pain relief and lowers opioid intake, doctors should think about concomitant anti-emetic prophylaxis to minimize side effects.

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