"COMPARISON BETWEEN LOW-DOSE KETAMINE & DEXMEDETOMIDINE ON INTRAOPERATIVE OPIOID REQUIREMENT IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES – A RANDOMISED CONTROL TRIAL"

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LIST OF ABBREVIATIONS

ADH	Antidiuretic hormone
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CBF	Cerebral blood flow
$CMRO_2$	Cerebral metabolic rate of oxygen
CO	Cardiac Output
CO_2	Carbon dioxide
DBP	Diastolic Blood Pressure
EEG	Electroencephalography
FRC	Functional Residual Capacity
HR	Heart Rate
HS	Highly significant
IAP	Intra-abdominal pressure
ICP	Intracranial pressure
MAP	Mean Arterial Pressure
NBM	Nil by mouth
NMDA	N-methyl-D-aspartate
NS	Not significant
PACU	Post Anaesthesia Care Unit
PONV	Postoperative nausea and vomiting
S	Significant
S.D.	Standard deviation
SBP	Systolic blood pressure
SVR	Systemic vascular resistance
SV	Stroke volume
VAS	Visual analogue scale
VS	Very Significant

ABSTRACT

Title of the article: Comparison between Low-Dose Ketamine & Dexmedetomidine on intraoperative opioid requirement in patients undergoing laparoscopic surgeries – A Randomised Control Trial

Context: Opioids are crucial for perioperative pain management but have significant side effects. This study explores the opioid-sparing effects of low-dose Ketamine versus Dexmedetomidine in laparoscopic surgery patients.

Aims: To compare low-dose Ketamine and Dexmedetomidine's impact on intraoperative opioid requirements and postoperative pain and nausea.

Settings and Design: A randomized control trial at KLES Prabhakar Kore Hospital & Medical Research Centre included 60 ASA I and II patients, aged 18-60, undergoing laparoscopic surgeries. Patients received low-dose Ketamine (0.2 mg/kg bolus, 0.2 mg/kg/hr infusion) or Dexmedetomidine (1 µg/kg bolus, 0.4 µg/kg/hr infusion).

Methods and Material: Sixty patients were randomized into Ketamine (Group K) or Dexmedetomidine (Group D). Parameters such as opioid consumption, hemodynamic stability, and pain levels were measured. Hemodynamic parameters were recorded at intervals, and postoperative pain was assessed using the Visual Analog Scale (VAS). Statistical analysis compared results.

Statistical analysis used: Variables were analysed using mean and standard deviation, unpaired and paired t-tests, Chi-square or Fisher's exact test, ANOVA, correlation, and regression.

Results: Group D required significantly less intraoperative Fentanyl and had more stable hemodynamics than Group K. Postoperative pain was significantly lower in

Group D at 1 and 2 hours post-surgery. No significant differences were found in postoperative nausea and vomiting.

Conclusions: Dexmedetomidine is more effective than Ketamine in reducing intraoperative opioid requirements and maintaining hemodynamic stability during laparoscopic surgeries. Its use in multimodal analgesia protocols can optimize pain management, reduce opioid consumption, and improve patient satisfaction and safety.

Key-words: Opioid-sparing, Ketamine, Dexmedetomidine, Laparoscopic surgeries, Perioperative pain

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INTRODUCTION

Opioids play a vital role in providing the analgesic component of anaesthesia during surgeries and also for postoperative pain management. They control pain by their action on multiple sites in the nervous system [1]. Though typically thought of as the ideal medication, opioids have a number of unfavourable side effects, including constipation, vomiting, nausea, and respiratory depression. [2].

Opioid-sparing approaches can alleviate the unwanted effects of opioids by enabling the use of the lowest opioid dose [3]. Multimodal regimens utilize a combination of medications with varying mechanisms of action, alongside nonpharmacological methods and techniques, to enhance the effectiveness of pain analgesia. The use of multiple analgesics thereby permits the use of lower & safer doses of each drug, which therefore minimises opioid related adverse effects [4,5].

Among the drugs used in opioid-sparing strategies, Ketamine is a NMDA receptor antagonist, plays a role in strategies for opioid-sparing. It is known for its potent analgesic properties, effectively reducing the need for opioids even at sub-anaesthetic doses. This reduction in opioid usage is particularly valuable in managing pain without the associated risks and side effects commonly linked to opioids. Moreover, Ketamine's administration in these lower doses minimizes the likelihood of adverse effects, making it a highly favourable option in pain management protocols. Its ability to provide substantial pain relief while mitigating opioid dependency highlights its importance in both clinical and surgical settings [6,7].

Dexmedetomidine is a α2-adrenergic agonist that offers multiple therapeutic benefits, including conscious sedation, anxiolysis, analgesic, and sympatholytic effects. When

administered intravenously during surgical procedures, dexmedetomidine has been shown to significantly reduce the need for rescue analgesia. Additionally, patients receiving dexmedetomidine experience lower levels of postoperative pain, which contributes to a more comfortable recovery process. This drug also helps in dipping the incidence of vomiting and nausea after surgery, further enhancing patient outcomes and overall satisfaction with the surgical experience. [8,9,10].

Both agents have been used in various capacities during the perioperative period, as sole/adjuvants to anaesthetic drugs, to improve intraoperative hemodynamics and postoperative recovery, yet their comparative impact on opioid consumption during laparoscopic surgeries warrants further investigation.

Hence an attempt is made in this study to examine the effects of Low-dose Ketamine and Dexmedetomidine in terms of effective intraoperative opioid requirement, in patients undergoing laparoscopic surgeries.

OBJECTIVES

Primary objective:

To compare between Low-dose Ketamine and Dexmedetomidine on the intraoperative opioid requirement.

Secondary objective:

to compare the post-operative pain and post-operative nausea and vomiting experienced by patients in both groups during laparoscopic procedures performed under general anaesthesia

REVIEW OF LITERATURE

The effectiveness of ketamine, a widely familiar anaesthetic agent, has been thoroughly investigated as adjunct to pain management in perioperative care. Randomized controlled trials and observational studies have demonstrated its efficacy in a number of operative settings.

AbdelRady et al. In their systematic review, (2021) have studied in depth impact of ketamine on analgesia and need of further analgesics for patients following intestinal surgeries. Before making the skin incision, participants in the trial received an intravenous (IV) ketamine at a dose of 1 mg/kg bolus. During the surgery, they received an IV infusion of 0.12 mg/kg of ketamine. The findings were significant: the ketamine group used less morphine after surgery, had a longer time until the first demand for extra pain relief and sores for pain for up to forty eight hours after surgery. In addition, these patients showed decreased surgical inflammation, fewer adverse events and greater satisfaction with the procedure in comparison to the group under control, demonstrating the analgesic outcomes of ketamine in this context.[11]

Similarly, Remérand et al. in 2009 evaluated the early and late painkilling effects of ketamine after total hip arthroplasty. The study involved administering an IV bolus of ketamine at the commencement of surgery, followed by a twenty four-hour infusion. The results indicated a significant decrease in postoperative morphine consumption, highlighting ketamine's role in enhancing postoperative pain management in orthopaedic surgeries.[12]

Further supporting these findings, Minoshima et al in (2015 investigated use of low-dose ketamine in “posterior correction surgery” for “adolescent idiopathic scoliosis”.

The study revealed that intra- and postoperative low-dose ketamine infusion significantly reduced postoperative morphine consumption, thus demonstrating its effectiveness in managing pain in paediatric spine surgeries.[13] This benefit was also observed by Sardeshpande and Deshmukh (2023), who reported that intravenous low-dose ketamine (0.15 mg/kg bolus followed by 0.12 mg/kg/hour) in abdominal surgeries extended the time until the first rescue analgesia was required and reduced the overall need for analgesics carrying minimal side effects.[14]

Ketamine's efficacy is further corroborated by studies in various surgical procedures. Ates et al in 2021 found that perioperative intravenous low-dose ketamine infusion during septorhinoplasty consistently reduced pain scores and opioid needs postoperatively, while also improving patient satisfaction.[15] Similarly, Honarmand et al. (2012) demonstrated that a preincisional ketamine bolus effectively provided 24-hour analgesia following appendectomy.[16]

In a comparative study by Mitra et al. (2017), both ketamine (administered as a 0.5 mg/kg bolus followed by a 250 mcg/kg/h infusion) and dexmedetomidine (administered as a 0.5 mcg/kg bolus followed by a 0.5 mcg/kg/h infusion) were found to be viable options as anaesthetic adjuvants to enhance postoperative analgesia in patients facing lumbar instrumentation surgery.[17]

Ahmad et al. (2023) highlighted that administering low-dose intravenous ketamine infusion during surgery yields effective postoperative pain relief while diminishing the requirement for opioid analgesics, making it a crucial component for optimizing postoperative pain management.[18]

Zhou et al. in 2022 conducted a systematic review and metaanalysis which revealed that perioperative administration of low-dose ketamine exhibited both analgesic

properties and a reduction in morphine usage following spine surgery. Importantly, this effect did not correlate with an increase in adverse events. However, this impact was not statistically significant in paediatric patients.[19]

Song et al. (2013) reported that ketamine did not decline PONV in patients undertaking lumbar spine surgery. Although ketamine had a detrimental impact on the severity of nausea, it effectively reduced postoperative fentanyl consumption in patients identified as high-risk for PONV.[20]

Kim et al. (2013) found that administering low-dose ketamine at a rate of two µg per kg per min following a bolus of 0.5 mg per kg, initated intraoperatively before skin inciision and continued for forty eight hours postoperatively, resulted in a notable reduction in overall fentanyl consumption during the forty eight hour period subsequent to lumbar spinal fusion surgery. This reduction was achieved without any discernible increase in adverse effects.[21]

Dexmedetomidine, another anaesthetic adjuvant, has also shown promise in postoperative pain management. Deepak et al. (2020) compared ketamine and dexmedetomidine in cervical spine surgery and found that both drugs reduced overall fentanyl consumption and pain scores, with ketamine demonstrating superior efficacy. This study highlighted the potential of dexmedetomidine as an effective agent for reducing postoperative opioid consumption and improving pain management outcomes.[22]

Chen et al. (2020) reported that dexmedetomidine contributed to lower doses of anaesthetic drugs and improved sedation and analgesic outcomes in gastric cancer surgeries. The study noted that dexmedetomidine maintained hemodynamic stability

and reduced intraoperative anaesthetic requirements, making it a valuable addition to anaesthetic protocols in major abdominal surgeries.[23]

Dexmedetomidine's benefits extend to various surgical contexts. For instance, Ramakrishnan et al. (2016) highlighted its efficacy in maintaining sedation and hemodynamic stability while reducing morphine requirements and respiratory depression in endotracheal tube tolerance. This study emphasized the dual benefits of dexmedetomidine in providing effective analgesia and maintaining stable intraoperative conditions.[24]

Trikhatri et al. (2018) observed that dexmedetomidine effectively mitigated the hemodynamic stress response during laparoscopic cholecystectomy and reduced postoperative analgesic needs. The study concluded that dexmedetomidine's ability to stabilize haemodynamics and reduce analgesic requirements makes it a suitable adjuvant in minimally invasive surgeries.[25] Additionally, Kundra et al. (2019) observed that dexmedetomidine infusion in lumbar spine surgery resulted in reduced intraoperative blood loss, and lower anaesthetic agent doses, further reinforcing its utility in complex surgical procedures.[26]

Meta-analyses and systematic reviews further reinforce the role of dexmedetomidine in perioperative pain management. Peng et al. (2014) found that dexmedetomidine enhances perioperative hemodynamic control and reduces opioid consumption and antiemetic needs during intracranial procedures, suggesting its benefits in neurosurgical settings.[27] Liu et al. in 2018 similarly reported that dexmedetomidine decreases operative opioids and after operative pain intensity at neurosurgery, highlighting its effectiveness in managing pain in patients undergoing neurosurgeries.[28]

Shalaby et al. (2018) concluded that dexmedetomidine outperformed fentanyl in maintaining hemodynamic stability and extending postoperative analgesia in laparoscopic cholecystectomy. This study's findings support the use of dexmedetomidine over traditional opioids for improved postoperative outcomes and patient satisfaction.[29]

Bakshi et al. (2020) demonstrated that intraoperative administration of dexmedetomidine reduced the need for opioids and inhalational anaesthetics during robotic oncologic surgeries. Despite these intraoperative benefits, the infusion did not provide significant postoperative advantages.[30] Fazel et al. (2020) also found that dexmedetomidine infusion during functional endoscopic sinus surgery decreased blood loss and reduced the consumption of morphine and pethidine.[31]

Manne et al. (2014) showed that a infusion of low-dosage of dexmedetomidine effectively weakens the haemodynamic stress response during laparoscopic surgery and reduces the need for postoperative analgesics.[32] Patel et al. (2020) compared dexmedetomidine and esmolol, finding that while both managed pressure responses during laparoscopic surgeries, dexmedetomidine was more effective in controlling HR and mean arterial pressure.[33]

Chavan et al in 2016 found that administering dexmedetomidine as an aide to general anaesthesia reduced stress responses during surgery and helped maintain hemodynamic stability without delaying recovery time.[34] Thakkar et al. (2021) similarly highlighted dexmedetomidine's efficacy in managing hemodynamic responses and reducing postoperative analgesic needs in laparoscopic surgeries.[35]

Song et al. (2016) demonstrated that intraoperative infusion of dexmedetomidine reduced cumulative morphine consumption and minimized adverse effects after

craniotomy.[36] Peng et al. (2015) supported these findings, showing that dexmedetomidine alleviated pain and reduced analgesic consumption following craniotomy.[37] Rajan et al. (2016) reported that dexmedetomidine provided better control of postoperative mean arterial pressure and enhanced analgesia compared to remifentanil during craniotomy.[38]

In conclusion, both low-dose ketamine and dexmedetomidine infusions have proven effective in providing postoperative analgesia with minimal side effects across various surgical contexts. These findings suggest that these agents are valuable additions to multimodal analgesia protocols, enhancing postoperative recovery and patient satisfaction. The accumulated evidence highlights the potential of these anaesthetic adjuvants in improving surgical outcomes and optimizing pain management strategies.

BASIC SCIENCES

LAPAROSCOPIC SURGERY

The laparoscopic approach has become a standard of care for many abdominal surgical procedures. Compared with laparotomy, laparoscopy allows smaller incisions, reduces the perioperative stress response, reduces postoperative pain, and results in shorter recovery time.

Anaesthetic concerns for patients undergoing laparoscopic and robotic surgery differ from those for patients undergoing open abdominal surgery.

Laparoscopy requires creation of a pneumoperitoneum by insufflation of gas, usually carbon dioxide (CO_2), to open space in the abdomen for visualization and surgical manipulation. CO_2 insufflation can be performed blindly using a Veress needle or by placement of a port under direct vision through a small subumbilical incision. The gas source is connected to the needle or port; intraabdominal pressure (IAP) is monitored as gas is insufflated, aiming for a pressure ≤15 mmHg to minimize physiologic effects.

Physiologic effects of the pneumoperitoneum, absorption of CO_2, and positioning required for surgery can influence intraoperative care and outcomes. In addition, some laparoscopic procedures take longer than the open alternative.

PHYSIOLOGICAL EFFECTS OF LAPAROSCOPY

Cardiovascular changes —

Table 1: Cardiovascular changes during laparoscopy [39,40,41]

Parameters	Change	Causes

Systemic vascular resistance and mean arterial pressure	Increased	• Hypercarbia • Neuroendocrine response (ie, increased catecholamines, vasopressin, and cortisol) • Mechanical factors (ie, direct compression of aorta)
Cardiac filling pressures	Increased	• Increased intrathoracic pressure secondary to pneumoperitoneum. • Increased sympathetic output due to neuroendocrine response and hypercarbia
Cardiac filling volumes	Variable; increased or no change	Interaction among: • Increased intravascular volume resulting from compression of liver and spleen • Reduced preload and venous return • Positioning • Patient's preexisting status
Cardiac index	Variable; decreased or no change	Interaction among: • Increased afterload • Decreased venous return • Decreased cardiac filling • Increased intravascular volume • Positioning • Patient's preexisting status
Cardiac rhythm	Bradyarrhythmias	Peritoneal stretch - vagal
	Tachyarrhythmias	• Hypercarbia • Hypoxia • Capnothorax • Pulmonary embolism

These effects are generally well tolerated by healthy patients. However, significant intraoperative cardiac dysfunction can occur in older patients and in those with cardiopulmonary disease (eg, chronic obstructive pulmonary disease [COPD], congestive heart failure, pulmonary hypertension, valvular heart disease).

Studies of hemodynamic events during laparoscopy in patients with significant cardiopulmonary disease have reported an increase in mean arterial pressure (MAP), systemic vascular resistance (SVR), and central venous pressure (CVP), with decreases in cardiac output (CO) and stroke volume (SV) during peritoneal insufflation [42,43,44,45,46].

Compared with healthy patients, those with cardiopulmonary disease may require more pharmacologic interventions and more intensive monitoring to respond to these changes.

Cardiovascular changes during laparoscopy relate to the increase in intraabdominal pressure (IAP) associated with carbon dioxide (CO_2) insufflation, effects of positioning, and of absorption of CO_2, as follows:

- **Effects of pneumoperitoneum:** Pneumoperitoneum and the associated increase in IAP result in neuroendocrine and mechanical effects on cardiovascular physiology.
    - Neuroendocrine effects – Increase in IAP results in catecholamine release and activation of the renin–angiotensin system with vasopressin release [9,10,11]. This increases MAP in most patients and may contribute to increases in SVR and pulmonary vascular resistance (PVR) [47].

      Vagal stimulation, from insertion of the Veress needle or peritoneal stretch with gas insufflation, can result in bradyarrhythmias.

Bradycardia is common in this setting, while atrioventricular dissociation, nodal rhythm, and asystole have been reported [48].

- Mechanical effects – Mechanical aspects of laparoscopy are dynamic; the resulting cardiovascular effects depend on the patient's preexisting volume status, insufflation pressure, and position. Compression of arterial vasculature with pneumoperitoneum increases SVR and PVR, with variable effects on CO and blood pressure (BP) [49,50,51].

  Hypercarbia caused by CO_2 absorption may also increase SVR and PVR; in most cases, minute ventilation is increased to prevent hypercarbia, but the increase in intrathoracic pressure that accompanies ventilator adjustments may further increase SVR and PVR.

  Cardiovascular effects tend to resolve quickly as pneumoperitoneum is maintained.

- **Effects of positioning:** Laparoscopic surgery is often performed in head-up (eg, for cholecystectomy) or head-down (eg, pelvic surgery) positions to allow the intraabdominal organs to fall away from the surgical field. Extremes of position can affect cardiovascular function.
  - Head up – The head-up position (ie, reverse Trendelenburg) leads to venous pooling, tends to reduce venous return to the heart [50,52], and may result in hypotension, especially in patients who are hypovolemic.
  - Head down – The-head down position (ie, Trendelenburg) position increases venous return and cardiac filling pressures [53].

- **Effects of hypercarbia:** Absorption of CO_2 during laparoscopy can have direct and indirect cardiovascular effects. The direct effects of hypercarbia and associated acidosis include decreased cardiac contractility, sensitization to arrhythmias, and systemic vasodilation. Indirect effects are the result of sympathetic stimulation, and include tachycardia and vasoconstriction, which may counteract vasodilation [50].

Pulmonary changes —

Pneumoperitoneum with CO_2 and surgical positioning are associated with changes in pulmonary function and gas exchange:

Table 2: Pulmonary changes during laparoscopic surgery [39]

Parameter	Change	Causes
Lung volume (ie, functional residual capacity)	Decrease	• Elevation of diaphragm • Increased intraabdominal pressure • Positioning
Lung compliance	Decreased Increased pleural pressure Increased airway pressure	• Elevation of diaphragm • Increased intraabdominal pressure
PCO_2	Increased, depending on ventilation	CO_2 absorption
PO_2	Variable	Interaction among: • Atelectasis • Hypoxic pulmonary vasoconstriction • Preoperative pulmonary status

Tracheal position	Cephalad displacement, possible mainstem intubation	• Increased intraabdominal pressure • Trendelenburg position

These changes can result from increased IAP with pneumoperitoneum and from absorption of CO_2.

During laparoscopy, minute ventilation must be increased to compensate for absorption of CO_2. Hyperventilation may be difficult for patients with COPD, asthma, and/or severe obesity, especially in Trendelenburg position. In patients with COPD and in older patients, end-tidal CO_2 ($ETCO_2$) may not accurately reflect arterial partial pressure of CO_2; in such patients, arterial blood gases may be required to monitor ventilation.

The absorption and elimination of CO_2 in patients with severe obesity appears to be similar to patients without obesity [54]. Arterial oxygenation decreases and alveolar–arterial oxygen gradient increases in anesthetized patients with obesity when placed in Trendelenburg position, though CO_2 insufflation tends to slightly reverse these effects [55].

- **Changes in pulmonary mechanics** – Pneumoperitoneum causes cephalad displacement of the diaphragm and mediastinal structures, which reduces functional residual capacity (FRC) and pulmonary compliance, resulting in atelectasis and increased peak airway pressures. These effects are exacerbated with steep Trendelenburg positioning (eg, during pelvic surgery) and are reduced with reverse Trendelenburg positioning (eg, during cholecystectomy

and gastric surgery). The changes in pulmonary compliance may be less with retroperitoneal insufflation (eg, during renal or adrenal procedures) compared with intraperitoneal insufflation

- **Ventilation/perfusion matching** – The reduction in FRC and atelectasis associated with laparoscopy may theoretically lead to shunting and ventilation/perfusion mismatch; however, in healthy patients, these effects are minimal and well tolerated, even with steep Trendelenburg positioning [41,53,56].

- **Endotracheal tube position** – Pneumoperitoneum and Trendelenburg positioning may cause cephalad movement of the carina, which can result in mainstem endobronchial migration of the endotracheal tube, hypoxia, and high inspiratory pressure [57,58]. In addition, endotracheal tube cuff pressure increases in some patients during laparoscopy [59].

Regional circulatory changes –

- **Splanchnic blood flow** – The mechanical and neuroendocrine effects of pneumoperitoneum can decrease splanchnic circulation, resulting in reduced total hepatic blood flow and bowel perfusion. However, hypercapnia can cause direct splanchnic vasodilatation. Thus, the overall effects on splanchnic circulation are not clinically significant [60,61].

- **Renal blood flow** – The creation of a pneumoperitoneum results in reduction in renal perfusion and urine output associated with renal parenchymal compression, reduced renal vein flow, and increased levels of

vasopressin[62,63,64]. When IAP is kept under 15 mmHg, renal function and urine output generally normalize soon after pneumoperitoneum deflation, without histologic evidence of pathologic changes.

The effects of laparoscopy on renal function for patients with preexisting renal disease have not been studied. In most cases, we believe that the benefits of a minimally invasive surgical approach outweigh theoretical concerns about the effect of increased intraabdominal pressure on renal function.

- **Cerebral blood flow** – Increased intraabdominal and intrathoracic pressures, hypercarbia, and Trendelenburg positioning can all increase cerebral blood flow (CBF) and intracranial pressures (ICP) [65]. In healthy patients undergoing prolonged pneumoperitoneum and steep Trendelenburg position, cerebral oxygenation and cerebral perfusion remain within safe limits [66]. In patients with intracranial mass lesions or significant cerebrovascular disorders (eg, carotid atherosclerosis and cerebral aneurysm), the increase in ICP may have clinical consequences. Therefore, in this patient population, we maintain strict normocapnia during laparoscopy.
- **Intraocular pressure** – Intraocular pressure (IOP) increases with pneumoperitoneum and increases further when the patient is positioned in Trendelenburg [67,68,69].

KETAMINE [70]

Pharmacology:

The ketamine molecule [2-(O-chlorophenyl)-2-methylamino cylohexanone] has a molecular

weight of 238. The racemic mixture is prepared in a slightly acidic solution (pH 3.5–5.5), is freely water-soluble, and has a pKa of 7.5. There is a chiral centre with two optical isomers (enantiomers).

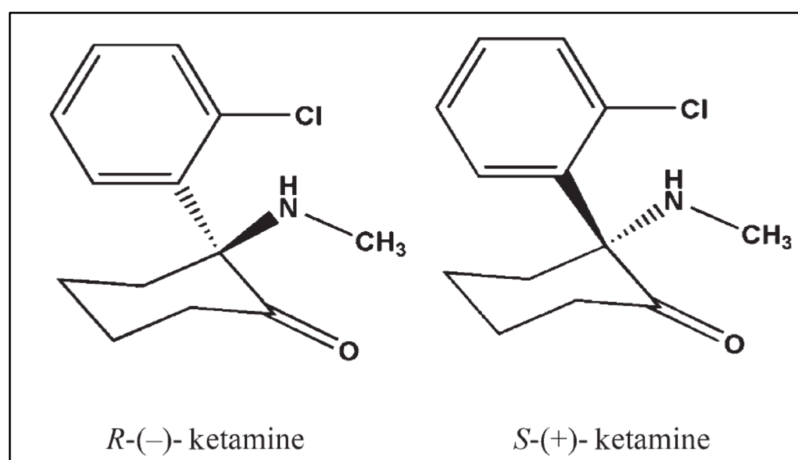


Figure 1: The optical isomers of Ketamine

Ketamine has a high lipid solubility (5–10 times that of thiopental) and crosses the blood-brain barrier faster. It undergoes demethylation and hydroxylation of the cyclohexanone ring. The metabolites are conjugated and excreted in the urine. Norketamine has 20–30% of the activity of the parent compound.[71] Its other pharmacokinetic attributes are detailed in this table:

Table 3: Pharmacokinetics of ketamine

Volume of distribution	3 litre kg^{-1}
Onset of action (i.v.)	30 s

Bioavailability (i.m.)	93%
Bioavailability (intranasal)	25–50%
Bioavailability (oral)	20–25%
Protein binding	20–50%
Distribution half life	10 min
Elimination half life	2–3 h
Site of metabolism	Liver: cytochrome P450
Metabolites	Norketamine, dehydronorketamine

Mechanism of action:

Ketamine acts on the central nervous system (CNS) and has local anaesthetic properties. Its effects are mediated primarily by noncompetitive antagonism at the N-methyl-Daspartate (NMDA) receptor Ca^{2+} channel pore. NMDA channel block appears to be the primary mechanism of the anaesthetic and analgesic action of ketamine (at the CNS and at spinal cord receptors). In addition, it reduces the presynaptic release of glutamate. The S (+) enantiomer has a three- to four-fold greater affinity for the NMDA receptor than the R(-) form.[72]

Other mechanisms of action of ketamine include interaction with opioid receptors, with a preference for mu and kappa receptors; this interaction with opioid receptors is complex. The affinity of ketamine for these receptors is 10 times less than that for the NMDA channel, and it has been confirmed in humans that naloxone does not antagonize the analgesic effects of ketamine. There is also evidence that ketamine has an antagonistic interaction with monoaminergic, muscarinic, and nicotinic receptors. Indeed, ketamine produces anticholinergic symptoms (e.g. tachycardia and

bronchodilatation). Ketamine at high doses has local anaesthetic properties; these may be through its ability to inhibit neuronal sodium channels.

Isomers:

The chiral centre of the cyclohexanone ring permits the existence of two enantiomers. Ketamine enantiomers exhibit pharmacological and clinical differences.

S-(+)-ketamine has greater affinity than R-(-)-ketamine at phencyclidine binding sites on the NMDA receptor. There are no significant differences in pharmacokinetic properties between enantiomers and the racemic mixture.[72] S-(+)-ketamine has been shown to be twice as potent as the racemic mixture in producing anaesthesia and analgesia, and thrice as potent as R-(-)–ketamine.[72] Animal studies suggest that the R-(2) enantiomer of ketamine is a more potent relaxant of acetylcholine induced airway smooth muscle contraction than the S(+) enantiomer. This difference appears to be caused by differential actions on receptor linked calcium channels.[73] This may have implications in the management of patients with asthma.

Clinical studies have shown that the recovery time is reduced with S-(+)-ketamine compared with the racemic mixture. The incidence of psychological side-effects is the same with each at equal plasma concentrations. However, because a smaller dose of S-(+)-ketamine is required for anaesthesia, there are less psychological side-effects. Coupled with the quicker recovery, patient acceptance of S-(+)-ketamine is greater. S-(+)-ketamine is significantly more expensive than the generic, racemic ketamine.

CNS Effects:

Ketamine produces the so-called 'dissociative' anaesthetic state that has been described as functional and electrophysiological dissociation between the thalamo-neocortical

and limbic systems. The EEG demonstrates a dominant theta activity with abolition of alpha rhythm. The unique clinical state produced by ketamine is typically a state of catalepsy in which the eyes remain open with a slow nystagmic gaze, whereas the corneal and light reflexes remain intact. Varying degrees of hypertonus and occasional purposeful movements unrelated to painful stimuli are noted in the presence of adequate surgical anaesthesia. Studies have demonstrated excitatory activity in both the thalamus and limbic systems without clinical evidence of seizure activity after ketamine administration. Thus, ketamine would be unlikely to precipitate convulsions in patients with seizure disorders and, in fact, experimental data suggest that ketamine has anticonvulsive and even neuroprotective properties [74]. Analgesia occurs at considerably lower blood concentrations than does the loss of consciousness. This is true for the racemic mixture and for S-(+)-ketamine.

Ketamine increases cerebral metabolism, cerebral blood flow (CBF), and intracranial pressure (ICP). The effect of S-(+)-ketamine on ICP is not yet known. The response of cerebral autoregulation to racemic ketamine has not yet been studied, but S-(+)-ketamine does not affect this autoregulation.[75] Pupillary dilatation, nystagmus, salivation, and lachrymation are common.

Emergence reactions:

Psychic sensations after ketamine emergence can be alterations in mood state and body image, floating sensations, vivid dreams or illusions, and occasional frank delirium. These dreams and illusions usually disappear on full wakening. However, it is important to discuss with patients these anticipated effects of ketamine. The incidence of psychic effects is approximately 5–30%. A higher incidence is associated with factors such as increasing age, female gender, patients who normally dream, rapid

intravenous administration, and large doses. Ketamine has been observed to activate psychoses in patients with schizophrenia. However, it has not been implicated in long-term psychotic reactions in patients without known psychiatric disease. Premedication can attenuate psychic reactions: midazolam (0.07–0.1 mg/kg), diazepam (0.15– 0.3 mg/kg), and lorazepam (2–4 mg) i.v. have been shown to be effective. The incidence is also decreased when used in conjunction with other sedative hypnotics and general anaesthetics.

Cardiovascular effects:

Ketamine has a unique combination of cardiovascular effects. Its administration is usually associated with tachycardia, increased blood pressure, and increased cardiac output. The exact mechanism of this centrally mediated sympathetic response is still not known. However, in the absence of autonomic control, ketamine has a direct myocardial depressant effect, which is usually overridden by this central response. S-(+)-ketamine in equal doses produces similar haemodynamic side-effects. It is possible to reduce the undesirable cardiovascular effects by giving ketamine as a continuous infusion and use of a benzodiazepine.

Respiratory effects:

Ketamine has minimal effect on central respiratory drive, although a transient decrease in ventilation can occur after bolus administration. Ketamine is a bronchial smooth muscle relaxant, so it has a special role in intractable asthma. It improves pulmonary compliance and is as effective as halothane in preventing bronchospasm. But the S(+) enantiomer may not be as useful as the racemate for reasons mentioned earlier.

Ketamine increases salivary secretions, which can produce potential problems in children by causing upper airway obstruction. Although swallowing, cough, sneeze, and gag reflexes are relatively intact with ketamine, silent aspiration can occur. Laryngospasm is frequently cited as an adverse effect of ketamine, but it is rarely observed. Frequently, sonorous respirations mistaken for laryngospasm are actually because of airway positioning, and such breathing problems can be managed simply by repositioning the patient's head. True laryngospasm during ketamine sedation is usually caused by stimulation of the vocal cords by instrumentation or secretions. Secretions can be reduced by giving glycopyrrolate premedication.

Effects on other systems:

Ketamine has not been shown to have any adverse effects on hepatic and renal systems. Intraocular pressure is slightly increased after ketamine administration. Ketamine produces an increase in muscle tone and sometimes muscle spasms, although it has been safely used in myopathies and malignant hyperthermia. Variable effects on uterine tone have been reported. Other effects include emesis, transient rash, and agitation.

Presentation, dosage and routes of administration:

The commercial racemic solution of ketamine is a mixture of R (-) and S(+) isomers in equal amounts, available as 10, 50, and 100 mg/ml with a preservative, benzathonium hydrochloride. The optical isomer S-(+)-ketamine is available in 5 and 25 mg/ml concentrations. Ketamine can be administered i.v., i.m., orally, nasally, rectally, and the preservative-free solution epidurally. The dose depends on the route of administration and the desired therapeutic effect.

Induction of anaesthesia: *0.5–1.5 mg/kg i.v. or 4–10 mg/kg i.m.*

Maintenance of anaesthesia: *10–30 mcg/kg/min via i.v. infusion*

Sedation and analgesia: *0.2–0.75 mg/kg i.v. or 2–4 mg/kg i.m, followed continuous infusion of 5–20 mg/kg/min with or without supplemental oxygen.*

Clinical applications

Sedation:

Ketamine is appropriate for children undergoing procedures in isolated situations. Emergence reactions in children are less intense, so it can be used for both sedation and general anaesthesia in procedures such as cardiac catheterization (with caution in patients with raised pulmonary vascular resistance), radiotherapy, radiological investigations, and burns dressings. Generally, subanaesthetic doses are required for minor procedures. Ketamine is often combined with premedication (e.g. benzodiazepines) to reduce the dose requirement and emergence reactions, and an antisialogogue (e.g. glycopyrrolate) to reduce salivary secretions.

In both adults and children, ketamine can be used as a supplement (i.v. or i.m.) during regional anaesthesia. It can also be given via the epidural route as an adjunct to a local anaesthetic to extend the duration of analgesia. Low-dose ketamine has also been used along with propofol to improve the quality of sedation. NMDA antagonists prevent the induction of central sensitization to painful stimuli. Ketamine is the only NMDA antagonist available; studies have demonstrated that small-dose perioperative administration of ketamine results in reduced postoperative opioid requirements[39] (40–60% on an average). Ketamine-treated patients also experienced less post operative nausea and vomiting.[39]

Induction and maintenance:

Ketamine has been extensively used in burns units for dressing changes, debridement, and skin grafting procedures in children and adults. Low-dose ketamine (l.5–2.0 mg/kg i.m) in these patents seems to have a rapid onset of action and produce good operating conditions, amnesia, and satisfactory analgesia with a rapid recovery. However, patients requiring repeated administration may develop tolerance.

High-risk patients with cardiorespiratory disorders (excluding ischaemic heart disease) represent prime candidates for ketamine anaesthesia. Extensive experience with ketamine in paediatric cardiac catheterizations has shown it to be highly effective with fewer catheter-associated arrhythmias than other general anaesthetics. Ketamine might be deleterious in patients with limited right ventricular functional reserve and increased pulmonary vascular resistance.

In patients with reactive airway disease, ketamine (racemate) can be useful as it produces bronchodilation and profound analgesia allowing administration of an increased inspired oxygen concentration.

Ketamine, if combined with a benzodiazepine or a benzodiazepine with an opioid, attenuates unwanted tachycardia, hypertension, and also postoperative psychomimetic reactions. This technique produces minimal haemodynamic perturbations, profound analgesia, dependable amnesia, and uneventful recovery.

Neurosurgery:

Historically, it has been believed that ketamine is contraindicated in patients with increased ICP, but reports of neuroprotective and even neuroregenerative effects have generated research into this topic.[74] Ketamine may prevent abnormal calcium ion fluxes or glutamate

accumulation through its interaction with NMDA receptors. The increase in CBF after ketamine administration is less than the increase in $CMRO_2$. S-(+)-ketamine reduced or maintained cerebral metabolism in most regions of the brain (experimental studies).[77]

Immunofunction:

Although ketamine has little effect on vascular endothelium, studies have demonstrated a significant reduction in leucocyte activation during hypoxaemia or sepsis.[78] Ketamine suppresses pro-inflammatory cytokine production in human whole blood in vitro.

DEXMEDETOMIDINE [79]

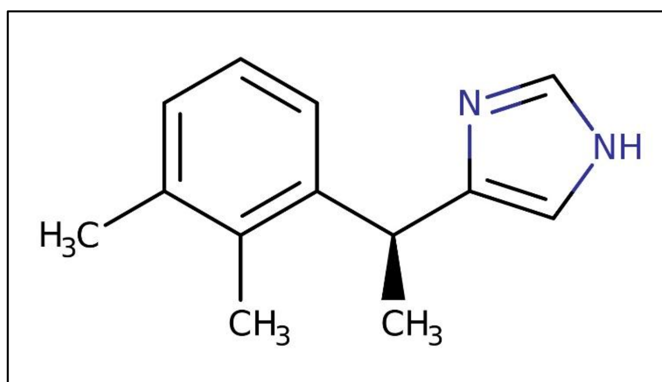


Figure 2: Chemical structure of Dexmedetomidine

Dexmedetomidine is the S-enantiomer of the veterinary sedative medetomidine. It is a highly selective α2-adrenoceptor agonist demonstrating an α2:α1 selectivity ratio of 1620:1. This makes it eight times more selective for the α2-adrenoceptor than clonidine.

Drug actions

Sedation and anxiolysis:

These properties are mediated via agonism of α2-adrenoceptors primarily in the locus coeruleus of the pons where it results in dose-dependent inhibition of norepinephrine release. It is postulated that this results in disinhibition of the ventrolateral preoptic nucleus which then releases inhibitory neurotransmitters. This pathway is part of the complex circuitry governing natural sleep, resulting in a quality of sedation with dexmedetomidine which more closely resembles normal physiological sleep than the more familiar GABA-ergic sedatives (propofol and the benzodiazepines). This sedation is characterized by preserved muscle tone and ventilation, by spontaneous and evoked movements, and by awakening by external stimuli. Once roused, patients are cooperative and can typically obey simple instructions. Once the external stimulus is discontinued, patients resume the previous level of sedation. Electroencephalogram

studies have further confirmed that the sedative effects of dexmedetomidine mimic stage 2 non-rapid eye movement sleep.[80]

Analgesia:

It is likely that dexmedetomidine exerts effects at various sites in the pain pathway, but its main site of action is at the level of the spinal cord where stimulation of α2-receptors in the substantia gelatinosa of the dorsal horn reduces the release of nociceptive neurotransmitters such as substance P.

Effects on organ systems:

The cardiovascular effects of the drug are biphasic. At higher rates of infusion, such as during administration of a loading dose, the predominant effect is hypertension due to activation of α2B receptors on vascular smooth muscle. This is superseded by hypotension and bradycardia as a result of the centrally mediated inhibition of sympathetic outflow. Case reports of bradycardia leading to asystole after loading dose administration of the drug in conjunction with multiple other be found in the literature.[81] Cardiovascular adverse effects associated with dexmedetomidine may be expected to be more pronounced in hypovolaemic patients, in those with diabetes mellitus or chronic hypertension, in the elderly and in those with high vagal tone.

A defining feature of the sedative action of dexmedetomidine is its minimal effect on ventilation, even when given in doses 10 times the maximum recommended.[82] In addition, MRI studies have shown that the airway remains patent during dexmedetomidine sedation.

Owing to actions on peripheral α2-adrenoecptors, dexmedetomidine also has decongestant and antisialagogue effects. It may theoretically reduce bowel motility.

Dexmedetomidine suppresses shivering, possibly due to agonism of α2B receptors in the hypothalamus. It exerts a diuretic effect by inhibiting the action of ADH at the collecting duct.

Despite its imidazole structure, dexmedetomidine has not been found to cause any clinically significant adrenal suppression.

Pharmacokinetics:

Administration is possible via multiple routes, with a bioavailability of 16% when given orally, 65% nasally, and 82% buccally. It is 94% protein bound with the unbound drug freely crossing the blood–brain barrier to exert its central effects, with a distribution half-life of 6 min. It undergoes glucuronidation, hydroxylation, and N-methylation in the liver to inactive metabolites which are then renally excreted. Hepatic impairment therefore should prompt a dose reduction due to decreased protein binding and metabolism, while renal impairment and renal replacement therapy requires no dose adjustment. It has a terminal elimination half-life of ~2 h with clearance estimated at 39 litre/h. Its steady-state volume of distribution (118 litres) is increased in patients with low plasma albumin concentration, prolonging the terminal half-life and context-sensitive half-time in such patients. [83]

Drug administration:

The dexmedetomidine infusion is begun at an infusion rate of 0.7 μg kg−1 h−1 and is then adjusted according to response within the dose range 0.2–1.4 μg kg−1 h−1. In contrast to its use in anaesthesia, it is recommended that no loading dose is given when used for sedation in the ICU. After dose adjustment, a new steady- state sedation level may not be reached for up to 1 h.

Perioperative use

Sedative premedication:

Its anxiolytic, sedative, sympatholytic, and antisialagogue properties, along with a lack of respiratory depression make dexmedetomidine suitable for premedication. The drug also acts as an anaesthetic-sparing agent and obtunds the pressor response to intubation. Its versatility in route of administration is an advantage in paediatric premedication where intranasal administration of 1 μg kg−1 dexmedetomidine was shown to be as effective a sedative as midazolam 0.5 mg kg−1 orally, with modest haemodynamic effects.[84]

Anaesthetic and opioid-sparing agent:

Dexmedetomidine decreases anaesthetic requirements and is opioid sparing. These properties are particularly useful in certain patient populations where the respiratory-depressant properties of opioids may be particularly detrimental, such as in bariatric surgery.

Sympatholysis:

A Cochrane review in 2009 [85] examined the theoretical benefits of α-agonists in obtunding the perioperative stress-induced increase in sympathetic activity, and thereby reducing cardiac complications of surgery. The authors found that perioperative α2-agonists reduced mortality and myocardial ischaemia, with the greatest benefit seen in patients undergoing vascular surgery. There was, however, an increase in perioperative hypotension and bradycardia with drug administration. Continuous infusion of dexmedetomidine throughout the extubation period has been used for emergence

smoothing. The drug also offers effective prevention and treatment of emergence phenomena.

Postoperative analgesia:

Postoperative dexmedetomidine infusions have been used to supplement other forms of analgesia in patients in whom opioid-induced respiratory depression would be potentially deleterious. A small randomized controlled trial of thoracic surgical patients found less supplemental epidural opioid was needed in the group who also received an i.v. dexmedetomidine infusion.

Neuroanaesthesia:

Dexmedetomidine is routinely used in our centre for neurosurgical procedures requiring intraoperative patient cooperation, that is, awake craniotomy for supratentorial tumour resection or deep brain stimulator implantation. It does not suppress epileptiform activity in patients undergoing electrocorticography and so is useful in epilepsy surgery.

Dexmedetomidine administration has no effect on intracranial pressure. Although therewere initial concerns that it may reduce cerebral blood flow leading to ischaemia, multiple studies have demonstrated a matched reduction in cerebral blood flow and cerebral metabolic rate.[86] It does not affect somatosensoryevoked potentials or motor-evoked potentials and so may be a useful anaesthetic-sparing agent and analgesic supplement in scoliosis surgery. Experimental studies show dexmedetomidine has neuroprotective effects in hypoxic–ischaemic and traumatic brain injury models. This neuroprotection appears to be afforded by the action of the drug on α2A-receptors and at imidazoline receptors.

Regional anaesthesia adjuncts:

A limited number of studies have shown a prolongation of regional nerve block when dexmedetomidine was added to the local anaesthetic.

General anaesthesia single-agent case reports:

There have been case reports of the use of dexmedetomidine as a sole agent for general anaesthesia. These patients required doses of 5–10 $\mu g\ kg^{-1}\ h^{-1}$ (5 to 10 times the maximum recommended for procedural sedation) to be adequately anaesthetized. Dexmedetomidine allowed preservation of respiratory drive with easy maintenance of a patent airway.

MATERIALS AND METHODS

Source of Data: Patients between the age group of 18-60 years, of either gender, belonging to "American Society of Anaesthesiologists (ASA) grade I" & "II", undergoing laparoscopic surgeries under General anaesthesia, at "KLES Prabhakar Kore Hospital & Medical Research Centre, Nehru Nagar, Belagavi".

Study Design: Randomised control trial

Study Period: One year

"**Sample Size:** The minimum sample size formula based on mean and standard deviation is:"

$$\text{"}n = \frac{(z_\alpha+z_\beta)^2(s_1{}^2+s_2{}^2)}{(\bar{X}_1-\bar{X}_2)^2}\text{"}$$

"Where $z\alpha$ is linked with the level of significance and $z\beta$ is linked with the power of the test. For 5% level of the significance $z\alpha$ =1.96 and $z\beta$ =0.84 for 80% power of the test."

Ref: "Wahdan AS, Mohamad M M, Helmy NY, Shehata GH, Salama AK. Effects of Low-Dose Ketamine Infusion on Alleviating the Opioid Burden for Patients Undergoing Myomectomy Surgery. Turk J Anaesthesiol Reanim 2021; 49(1): 52-7."

The parameter considered in the calculation was post operative opioid consumption.

" $\bar{X}_1$ is the mean of the first group (16.34) and $\bar{X}_2$ is the mean of the second group (18.4).

s1 is the standard deviation of the first group (3.0) and s2 is the standard deviation of the second group (2.32)."

"With these values the sample size obtained was 30."

"There were two groups with 30 cases in each group."

Sampling technique: Patients was assigned randomly to the Low-dose Ketamine and Dexmedetomidine groups using a random method of allocation.

For this purpose, the first patient was assigned to one group using coin tossing and then, the next patient would be assigned to the other group. The distributions remained hidden to the patients.

Inclusion Criteria:

- Age: Eighteen to sixty years
- "ASA I" and "II" patients
- Patients who are undertaking laparoscopic general anaesthesia surgeries

Exclusion Criteria:

- Individuals who are allergic to any of the study substances
- "ASA III" and above
- BMI >45
- History of epilepsy
- Patients with cardiac, renal or liver disease

Study protocol:

Following agreement and approval from the Clinical Trials Registry of India, the Institutional Review Board, and the Institutional Ethical Committee, a total of sixty patients undergoing general anaesthesia were included in the study.

Following the fulfilment of inclusion and exclusion requirements and the acquisition of informed consent, patients were randomised into two groups:

Group K: Patients were administered an intravenous bolus of Ketamine 0.2mg/kg followed by 0.2mg/kg/hr of Ketamine as an intravenous infusion.

Group D: Patients were administered an intravenous bolus of Dexmedetomidine 1µg/kg followed by 0.4µg/kg/hr of Dexmedetomidine as an intravenous infusion.

A detailed Pre-Anaesthetic Evaluation & investigations were done, 1 day prior to surgery. Both the group patients were instructed for NBM for 8 hours.

An 18G cannula was secured & fluids at 5mL/kg/hr was given to all patients in pre-operative room.

All of the standard monitors were connected once the patients were moved to the operating room.

After being preoxygenated for three minutes, each patient received an injection of fentanyl (2µg/kg iv), midazolam injection at 0.05 milligram per kg iv), and glycopyrrolate injection at 0.005 milligram per kg iv).

Injections of propofol (2 mg/kg iv) and scoline (2 mg/kg iv) were used to induce both groups. An endotracheal tube of the proper size was then inserted.once sufficient muscle relaxation was confirmed. The patient was then placed on mechanical ventilation

Both groups received Isoflurane, along with Nitrous oxide, oxygen, Vecuronium, and controlled ventilation with 6–8 millilitres per kg tidal volume, and the Normocapnia was attained by adjusting the breathing rate.

5 minutes after creation of pneumoperitoneum, Patients under Group K received intravenous bolus of Ketamine 0.2 mg/kg followed by 0.2 mg/kg/hr as intravenous infusion, till the end of surgery. Patients under Group D received intravenous bolus of Dexmedetomidine 1µg/kg followed by 0.4µg/kg/hr as intravenous infusion.

During surgery, intraoperative haemodynamics including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) was recorded at 5 minutes, 10 minutes, 20 minutes, and every thirty minutes until the end of the surgery. If there were indications of insufficient pain relief, like an increase in MAP and HR by more than 20% from the pre-induction levels, extra intraoperative dose of Inj. Fentanyl 0.5µg/kg was given to both groups.

The administration of the study medications was halted at the conclusion of pneumoperitoneum.

Vecuronium, nitrous oxide, and isoflurane were stopped at the conclusion of the surgery. Glycopyrrolate injection (0.01 mg/kg iv) and neostigmine injection (0.05 mg/kg iv) were used to reverse the neuromuscular blockade. After the extubation conditions were met, the endotracheal tube was removed.

Following that, the patients were transferred to the postanesthesia care unit (PACU), where the VAS and their vital signs (MAP, HR, SBP, DBP, and MAP) were first evaluated. Every hour, these evaluations were conducted again. The patients' vital signs and pain levels were tracked every six hours for a total of twelve hours after they received their discharge from the PACU.

A standard postoperative analgesia regimen of 1g intravenous infusion of Paracetamol every 6 hours were given during the first 24 hours to each patient. Furthermore, boluses of Inj. Fentanyl 0.5µg/kg iv were given when the VAS was ≥4, in both groups.

The primary outcome was total Fentanyl requirement in intraoperative period and hemodynamic stability. Secondary outcomes were Fentanyl requirement in postoperative period and postoperative nausea & vomiting.

Data collection procedure:

Intraoperative hemodynamics, such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), were monitored during the procedure at five-minute, ten-minute, and twenty-minute intervals, and then every thirty minutes until the surgery had ended.

The patients were subsequently transferred to the postanesthesia care unit (PACU), where initial assessments of the VAS, vital signs (MAP, HR, SBP, DBP, and MAP), and hourly assessments were performed. The patients' vital signs and pain levels were checked every six hours for twelve hours after they were released from the PACU.

Data processing and analysis/statistical analysis:

"The study aimed to compare two groups. For continuous quantitative variables, the mean and standard deviation were calculated. Inter-group continuous variables were compared using appropriate statistical tools, such as the unpaired Student's t-test. Within-group comparisons of two quantitative variables were performed using the paired Student's t-test."

"Categorical data were expressed as rates, ratios, and percentages. The associations between outcomes, clinical, and demographic characteristics were assessed using the

Chi-square test or Fisher's exact test. Additionally, tools such as ANOVA, correlation, and regression analyses were employed as needed."

"Discrete variables were represented by their median values. Nonparametric tests were used for comparing discrete variables. Appropriate graphs were utilized to illustrate the comparisons. A p-value of less than 0.05 was considered statistically significant for all tests."

RESULTS

A total of sixty patients were comprehended in our study titled "Comparison between low-dose Ketamine and Dexmedetomidine on intraoperative opioid requirement in patients undergoing laparoscopic surgeries – A randomised control trial", where the patients were distributed into two groups, Group K and Group D of 30 each, and the following data was collected.

Table 4: Gender distribution of the participants:

	GROUP K		GROUP D	
GENDER	**NUMBER**	**%**	**NUMBER**	**%**
MALE	11	36.67	11	36.67
FEMALE	19	63.33	19	63.33
TOTAL	30	100.00	30	100.00

Graph 1: Graph depicting gender distribution of participants:

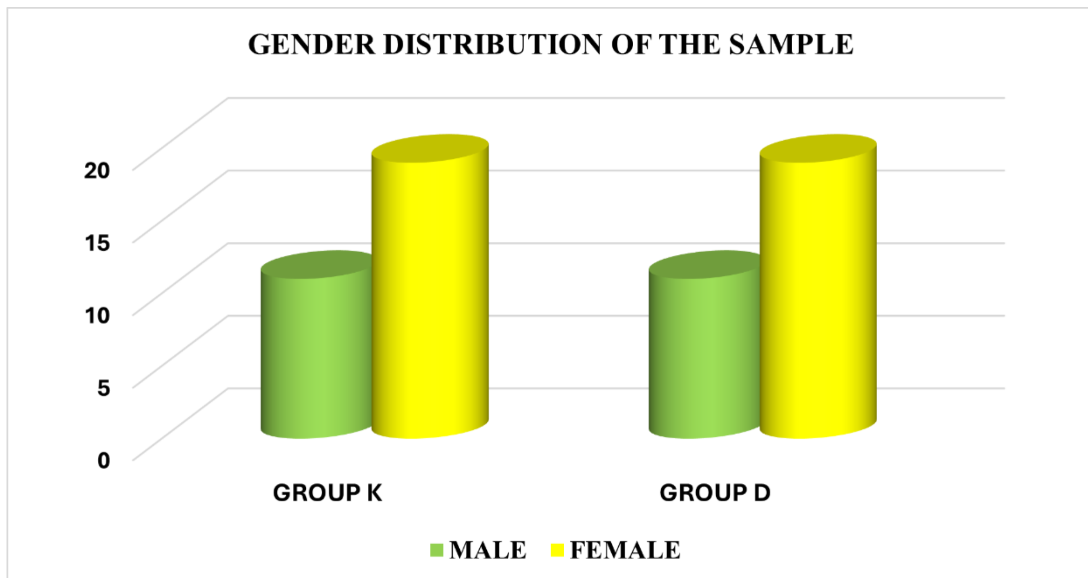


Table 5: Demographics:

	GROUP K		GROUP D	
AGE	**NUMBER**	**%**	**NUMBER**	**%**
< 20	1	3.33	0	0.00
20 - 29	8	26.67	3	10.00
30 - 39	11	36.67	4	13.33
40 - 49	4	13.33	7	23.33
50 - 59	6	20.00	8	26.67
60-69	0	0.00	8	26.67
TOTAL	30	100.00	30	100.00

Graph 2: Graph depicting age distribution of the participants:

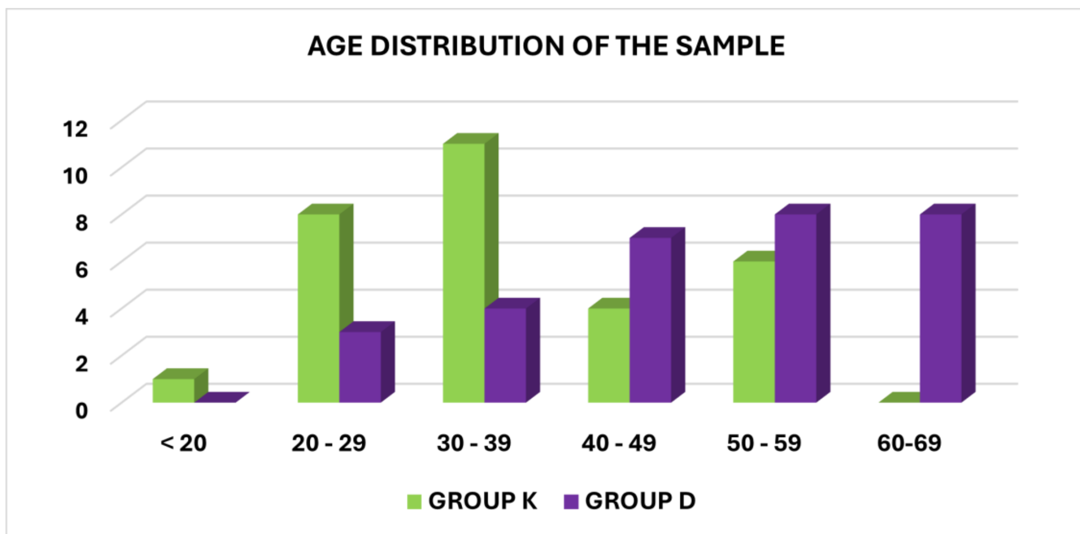


Table 6: Comparison of Age and Weight Between Groups K and D

	Group K				Group D					
	MEAN	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**p VALUE**	**INFERENCE**
AGE	36.13	11.24	18	56	47.87	12.30	22	60	0.0003	HS
WEIGHT	59.03	8.45	38	70	63.97	8.86	50	85	0.0313	S

The statistical analysis reveals that there are differences that were significant between groups K and D in terms of both age and weight. The age difference is highly significant, with group D being older on average. The weight difference is significant, with group D having a higher average weight

Table 7: Distribution of ASA Scores between Groups K and D with Chi-Square Test Analysis

ASA	GROUP K	GROUP D	TOTAL
1	23	15	38
2	7	15	22
TOTAL	30	30	60

For the above table the "p-value" is 0.0321.

This shows that there is a difference in the distribution of ASA scores between groups K and D. Specifically, Group K has a significantly larger number of ASA 1 cases compared to Group D.

Table 8: Comparison of Surgery Duration between Groups K and D

DURATION OF SURGERY (HRS)									
GROUP K				GROUP D					
MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
02:00	00:39	01:10	03:30	02:14	00:38	01:16	03:55	0.1766	NS

The analysis shows that the duration of surgery does not significantly differ between Groups K and D. Both groups have similar mean durations and ranges of surgery times. The p-value of 0.1766 confirms that the observed differences in surgery duration are not statistically significant.

Table 9: Comparison of Pneumoperitoneum Duration between Groups K and D

DURATION OF PNEUMOPERITONEUM (HRS)									
GROUP K				GROUP D					
MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
01:45	00:33	01:00	03:00	01:57	00:35	01:01	03:25	0.1664	NS

The analysis shows that the duration of pneumoperitoneum does not significantly differ between Groups K and D. Both groups have similar mean durations and ranges of pneumoperitoneum times. The p-value of 0.1664 confirms that the observed differences in pneumoperitoneum duration are not statistically significant.

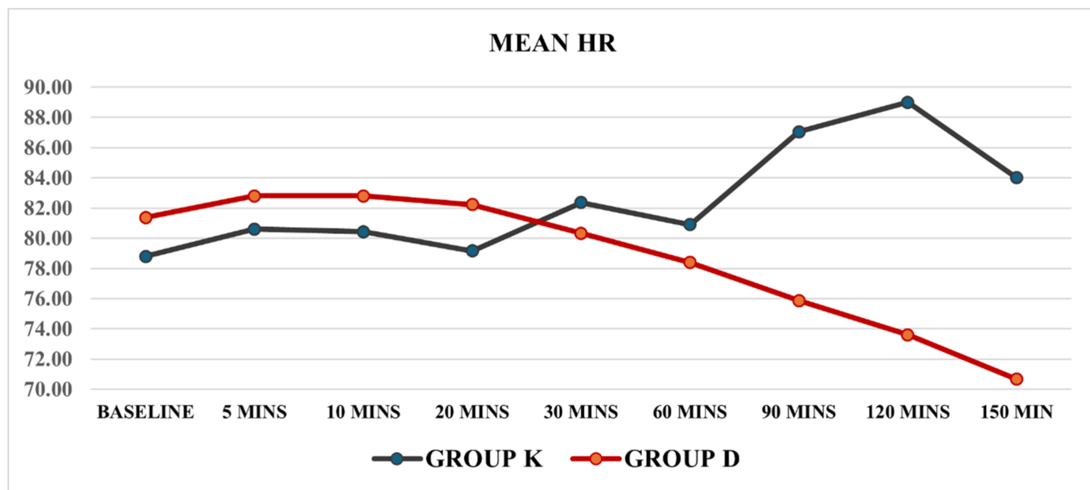
Table 10: Table showing Intraoperative Heart Rate Trends, comparing between the two groups, and comparison within each group with respect to baseline:

	GROUP K				GROUP D					
	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
BASELINE	78.80	9.58	62	100	81.37	9.39	66	102	0.2990	NS
5 MINS	80.60	8.47	62	94	82.80	7.49	68	100	0.2911	NS
10 MINS	80.43	9.93	62	96	82.80	7.75	64	98	0.3076	NS
20 MINS	79.17	16.68	9	100	82.23	6.57	64	96	0.3527	NS
30 MINS	82.37	9.29	64	100	80.33	6.54	64	94	0.3312	NS
60 MINS	80.90	8.35	64	94	78.40	6.46	62	88	0.1997	NS
90 MINS	87.05	12.95	68	110	75.87	6.44	64	88	0.0008	VS
120 MINS	89.00	12.37	68	106	73.62	7.11	60	90	0.0008	VS
150 MIN	84.00	12.65	64	96	70.67	5.16	62	76	0.0415	S

	GROUP K					
	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
BASELINE	78.80	9.58	62	100	--	--
5 MINS	80.60	8.47	62	94	0.2219	NS
10 MINS	80.43	9.93	62	96	0.2596	NS
20 MINS	79.17	16.68	9	100	0.4586	NS
30 MINS	82.37	9.29	64	100	0.0743	NS
60 MINS	80.90	8.35	64	94	0.1845	NS
90 MINS	87.05	12.95	68	110	0.0069	VS
120 MINS	89.00	12.37	68	106	0.0033	VS
150 MIN	84.00	12.65	64	96	0.1448	NS

GROUP D					
MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
81.37	9.39	66	102	--	--
82.80	7.49	68	100	0.2580	NS
82.80	7.75	64	98	0.2608	NS
82.23	6.57	64	96	0.3401	NS
80.33	6.54	64	94	0.3114	NS
78.40	6.46	62	88	0.0797	NS
75.87	6.44	64	88	0.0099	VS
73.62	7.11	60	90	0.0056	VS
70.67	5.16	62	76	0.0055	VS

Graph 3 : Graph showing Intraoperative mean Heart Rate trends:



Group K shows a trend of increasing HR over the intraoperative period, with significant peaks at 90 and 120 minutes. Whereas, Group D shows a trend of decreasing HR after an initial slight rise, with significant decreases at 90, 120, and 150 minutes.

The data suggests that Group K experiences a rise in HR during the procedure, while Group D experiences a reduction in HR over time.

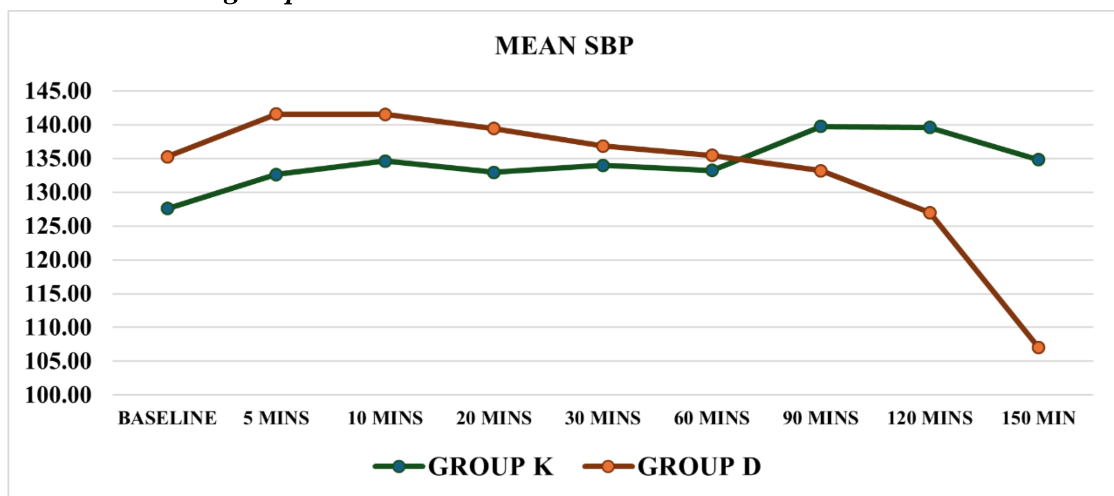
Table 11: Table showing Intraoperative SBP Trends, comparing between the two groups, and comparison within each group with respect to baseline:

	GROUP K				GROUP D					
	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
BASELINE	127.57	13.43	100	155	135.23	15.16	100	160	0.0426	S
5 MINS	132.63	12.57	110	160	141.57	12.85	116	162	0.0086	VS
10 MINS	134.63	13.49	106	160	141.53	13.76	106	161	0.0547	NS
20 MINS	132.97	13.28	106	161	139.43	12.31	110	160	0.0553	NS
30 MINS	133.97	13.77	110	162	136.83	15.55	104	176	0.4526	NS
60 MINS	133.23	15.97	108	170	135.47	13.87	102	178	0.5653	NS
90 MINS	139.74	20.18	110	188	133.17	14.37	104	164	0.2264	NS
120 MINS	139.58	18.43	118	170	127.00	12.18	102	150	0.0541	NS
150 MIN	134.80	18.95	112	164	107.00	46.69	12	130	0.2464	NS

	GROUP K					
	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
BASELINE	127.57	13.43	100	155	--	--
5 MINS	132.63	12.57	110	160	0.0684	NS
10 MINS	134.63	13.49	106	160	0.0233	S
20 MINS	132.97	13.28	106	161	0.0614	NS
30 MINS	133.97	13.77	110	162	0.0368	S
60 MINS	133.23	15.97	108	170	0.0711	NS
90 MINS	139.74	20.18	110	188	0.0072	VS
120 MINS	139.58	18.43	118	170	0.0119	S
150 MIN	134.80	18.95	112	164	0.1499	NS

GROUP D					
MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
135.23	15.16	100	160	--	--
141.57	12.85	116	162	0.0431	S
141.53	13.76	106	161	0.0486	S
132.97	13.28	106	161	0.1218	NS
136.83	15.55	104	176	0.3440	NS
135.47	13.87	102	178	0.4753	NS
133.17	14.37	104	164	0.3092	NS
127.00	12.18	102	150	0.0458	S
107.00	46.69	12	130	0.0044	VS

Graph 4: Graph showing Intraoperative mean Systolic Blood Pressure trends between the two groups:



Group K shows a trend of increasing SBP over the intraoperative period, with significant peaks at various time points. Whereas, Group D shows an initial rise in SBP, with significant peaks at 5 and 10 minutes, followed by a decrease, with a significant drop at 150 minutes.

The data suggests that both groups experience changes in SBP during the intraoperative period, with Group K generally showing increases and Group D showing an initial rise followed by a decrease.

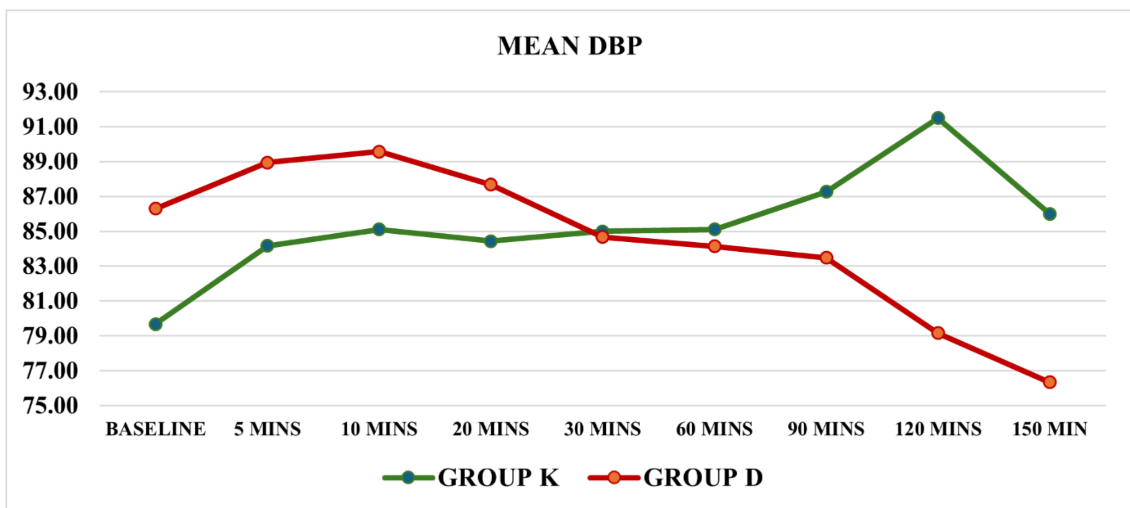
Table 12: Table showing Intraoperative DBP trends, comparing between the two groups, and comparison within each group with respect to baseline:

	GROUP K				GROUP D					
	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
BASELINE	79.67	11.55	60	120	86.30	10.11	60	107	0.0213	S
5 MINS	84.17	13.28	70	138	88.93	8.31	70	105	0.1011	NS
10 MINS	85.10	13.03	62	130	89.57	8.95	62	106	0.1272	NS
20 MINS	84.43	14.62	62	140	87.67	8.44	64	100	0.2985	NS
30 MINS	85.00	14.01	68	136	84.67	7.59	70	98	0.9092	NS
60 MINS	85.10	13.22	63	130	84.13	7.46	70	98	0.7286	NS
90 MINS	87.26	17.23	70	138	83.48	9.71	68	105	0.3755	NS
120 MINS	91.50	21.98	70	150	79.15	6.83	68	86	0.0660	NS
150 MIN	86.00	27.96	62	132	76.33	7.53	64	82	0.4334	NS

	GROUP K					
	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
BASELINE	79.67	11.55	60	120	--	--
5 MINS	84.17	13.28	70	138	0.0834	NS
10 MINS	85.10	13.03	62	130	0.0464	S
20 MINS	84.43	14.62	62	140	0.0832	NS
30 MINS	85.00	14.01	68	136	0.0565	NS
60 MINS	85.10	13.22	63	130	0.0477	S
90 MINS	87.26	17.23	70	138	0.0353	S
120 MINS	91.50	21.98	70	150	0.0138	S
150 MIN	86.00	27.96	62	132	0.1872	NS

GROUP D					
MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
86.30	10.11	60	107	--	--
88.93	8.31	70	105	0.1375	NS
89.57	8.95	62	106	0.0952	NS
87.67	8.44	64	100	0.2860	NS
84.67	7.59	70	98	0.2410	NS
84.13	7.46	70	98	0.1745	NS
83.48	9.71	68	105	0.1553	NS
79.15	6.83	68	86	0.0127	S
76.33	7.53	64	82	0.0145	S

Graph 5: Graph showing Intraoperative mean Diastolic Blood Pressure trends between the two groups:



Group K shows a trend of increasing DBP over the intraoperative period, with significant peaks at various time points. Whereas, Group D shows an initial slight rise in DBP, followed by a general decrease, with significant drops at 120 and 150 minutes.

The data suggests that Group K experiences an increase in DBP during the procedure, with significant elevations at several time points, whereas Group D shows a decrease in DBP over time, with significant reductions observed later in the intraoperative period.

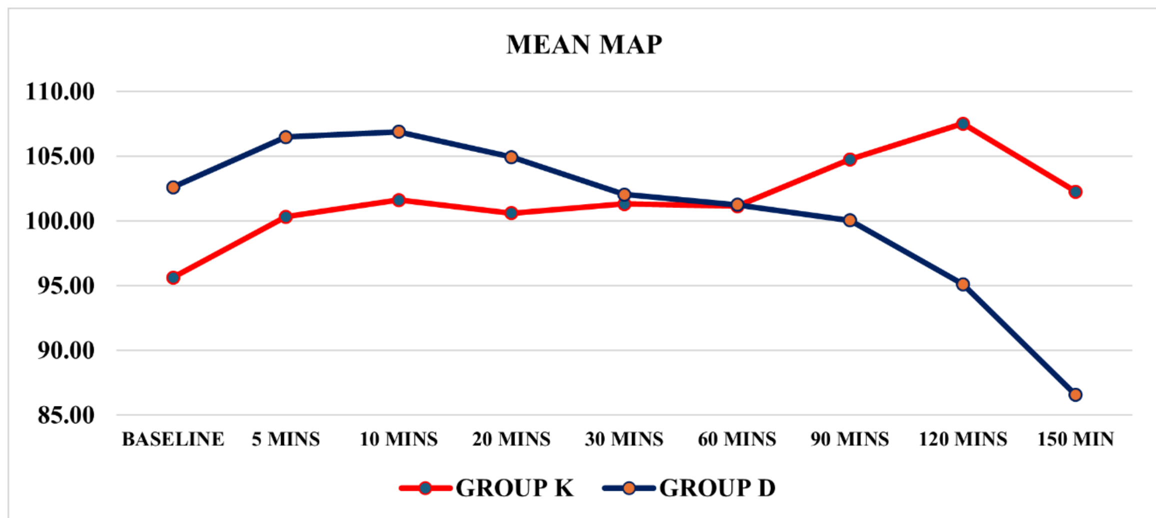
Table 13: Table showing Intraoperative Mean Arterial Blood Pressure trends, and comparison within each group with respect to baseline:

	GROUP K				GROUP D					
	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
BASELINE	95.63	10.51	73	120	102.61	11.42	73	123	0.0168	S
5 MINS	100.32	11.63	83	138	106.48	9.17	87	123	0.0265	S
10 MINS	101.61	11.36	82	130	106.89	9.56	80	123	0.0564	S
20 MINS	100.61	13.01	77	140	104.92	8.96	79	117	0.1403	NS
30 MINS	101.32	12.06	83	136	102.06	9.12	81	115	0.7915	NS
60 MINS	101.14	12.16	79	130	101.24	8.63	81	118	0.9708	NS
90 MINS	104.75	16.07	85	138	100.04	9.96	83	123	0.2518	NS
120 MINS	107.53	19.02	86	150	95.10	7.70	79	107	0.0403	S
150 MIN	102.27	21.48	79	132	86.56	19.96	47	98	0.2406	NS

	GROUP K					
	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
BASELINE	95.63	10.51	73	120	--	--
5 MINS	100.32	11.63	83	138	0.0534	NS
10 MINS	101.61	11.36	82	130	0.0193	S
20 MINS	100.61	13.01	77	140	0.0542	NS
30 MINS	101.32	12.06	83	136	0.0282	S
60 MINS	101.14	12.16	79	130	0.0327	S
90 MINS	104.75	16.07	85	138	0.0100	S
120 MINS	107.53	19.02	86	150	0.0065	VS
150 MIN	102.27	21.48	79	132	0.1375	NS

GROUP D					
MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
102.61	11.42	73	123	--	--
106.48	9.17	87	123	0.0768	NS
106.89	9.56	80	123	0.0606	NS
104.92	8.96	79	117	0.1934	NS
102.06	9.12	81	115	0.4179	NS
101.24	8.63	81	118	0.3015	NS
100.04	9.96	83	123	0.1979	NS
95.10	7.70	79	107	0.0184	S
86.56	19.96	47	98	0.0047	VS

Graph 6: Graph showing Intraoperative MAP trends between the two groups:



The data suggests that Group K experiences an increase in MAP during the procedure, with significant elevations at several time points, whereas Group D shows a decrease in MAP over time, with significant reductions observed later in the intraoperative period. These distinct patterns highlight different physiological responses between the two groups during surgery.

Table 14: Comparison of total rescue Fentanyl Administered Between Groups K and D

TOTAL FENTANYL ADMINISTERED (IN MG)									
GROUP K				GROUP D					
MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
30.67	3.87	25	35	22.50	3.54	20	25	0.0395	S

The information shows that the total amount of rescue fentanyl given to the two groups differs significantly. With a "p-value" of 0.0395, Group K's mean fentanyl dosage was greater than Group D's, a statistically significant difference.

Table 15: Comparison of Postoperative Pain Levels Between Groups K and D Using Visual Analog Scale (VAS) Scores

	IMMEDIATE				
VAS	GROUP K	GROUP D	TOTAL	p VALUE	INFERENCE
0	12	19	31	0.3514	NS
1	8	5	13		
2	5	3	8		
3	5	3	8		
TOTAL	30	30	60		

	1 HR				
VAS	GROUP K	GROUP D	TOTAL	p VALUE	INFERENCE
0	6	17	23	0.0127	S
1	13	10	23		
2	7	1	8		
3	4	2	6		
TOTAL	30	30	60		

	2 HR				
VAS	GROUP K	GROUP D	TOTAL	p VALUE	INFERENCE
0	4	14	18	0.0144	S
1	13	10	23		
2	9	6	15		
3	4	0	4		
TOTAL	30	30	60		

	3 HR				
VAS	GROUP K	GROUP D	TOTAL	p VALUE	INFERENCE
0	3	7	10	0.1597	NS
1	12	16	28		
2	12	6	18		
3	3	1	4		
TOTAL	30	30	60		

	6 HR				
VAS	GROUP K	GROUP D	TOTAL	p VALUE	INFERENCE
0	1	3	4	0.2998	NS
1	10	15	25		
2	15	10	25		
3	4	2	6		
TOTAL	30	30	60		

	12 HR				
VAS	GROUP K	GROUP D	TOTAL	p VALUE	INFERENCE
0	0	3	4	0.2006	NS
1	12	15	25		
2	13	8	25		
3	5	4	6		
TOTAL	30	30	60		

Overall Pain Management: Both groups show similar postoperative pain levels at most time points, with significant differences observed only at 1 and 2 hours post-surgery, where Group K reported higher pain levels compared to Group D.

1 Hour and 2 Hour Assessments: Group K experienced higher pain levels, suggesting possible differences in the effectiveness or duration of analgesia between the two groups during these periods.

Immediate, 3 Hour, 6 Hour, and 12 Hour Assessments: Pain levels were comparable between the groups.

Furthermore, among the sixty patients studied, there was no occurrence of post-operative vomiting or post-operative nausea.

DISCUSSION

“The current study aimed to compare the effects of low-dose Ketamine and Dexmedetomidine on intraoperative opioid requirements, hemodynamic stability, postoperative pain, and postoperative nausea and vomiting in patients undergoing laparoscopic surgeries.” “The study included a sample size of 60 patients, aged 18 to 60 years, all classified as ASA I or II. Our findings revealed significant differences in outcomes between the two groups, offering valuable insights into the efficacy of these anaesthetic adjuvants.”

Opioid Requirement:

The primary objective of this study was the total intraoperative Fentanyl requirement. The results demonstrated that patients in Group D (Dexmedetomidine) required significantly less Fentanyl compared to those in Group K (Ketamine). The mean total Fentanyl administered in Group D was 22.50 mg, compared to 30.67 mg in Group K, which is statistically significant (p=0.0395). This finding aligns with prior studies, such as those by Mitra et al. in 2017 and Garg et al. (2016), which also reported reduced opioid consumption with Dexmedetomidine compared to Ketamine.[17,87]

The opioid-sparing effect of Dexmedetomidine can be credited to its potent α2-adrenoceptor agonist properties, which enhance analgesia and sedation, reducing the need for additional opioid analgesics. Dexmedetomidine's ability to decrease opioid requirements is particularly beneficial, as it can help minimise opioid dependence and ADR associated with high opioid dosages.

Conversely, while Ketamine did not show the same level of opioid-sparing effect as Dexmedetomidine in this study, it still significantly contributed to analgesia.

Ketamine's mechanism, primarily through NMDA receptor antagonism, provides a unique analgesic pathway that can be particularly useful in certain clinical scenarios. Several studies have documented Ketamine's efficacy in reducing postoperative pain and opioid consumption, as noted in AbdelRady et al. (2021) and Remérand et al. (2009),[11,12] although these benefits were less pronounced in the present study's intraoperative context.

Hemodynamic Stability:

Cardiovascular metrics, including HR, SBP, DBP, and MAP, were closely monitored throughout the surgery. Our data indicate that Dexmedetomidine provides superior hemodynamic stability compared to Ketamine.

Heart Rate (HR): Group D exhibited a significant decrease in HR over time, whereas Group K showed an increase, especially at 90 and 120 minutes.

Systolic Blood Pressure (SBP): Group K showed a trend of increasing SBP over the intraoperative period, while Group D showed an initial rise followed by a decrease.

Diastolic Blood Pressure (DBP): Group K exhibited an increase in DBP during the procedure, with significant elevations at several time points. In contrast, Group D showed a decrease in DBP over time, with significant reductions observed later in the intraoperative period.

Mean Arterial Pressure (MAP): Group K experienced an increase in MAP during the procedure, with significant elevations at several time points, whereas Group D showed a decrease in MAP over time.

These results corroborate findings from previous research. For instance, Manne et al. (2014) and Patel et al in 2020 found Dexmedetomidine effectively attenuates

hemodynamic responses during laparoscopic surgeries.[32,33] This can be explained by Dexmedetomidine's sympatholytic effects, which help maintain stable blood pressure and heart rate by reducing sympathetic outflow and catecholamine release.

Ketamine is known to increase sympathetic tone, which can lead to elevated heart rate and blood pressure. This characteristic can be advantageous in patients who are at risk of hypotension, but it may pose a challenge in maintaining hemodynamic stability during surgery. Our findings reflect this, with Group K showing increased HR and BP levels intraoperatively. However, this increase can be managed with careful monitoring and appropriate dose adjustments, as Ketamine also provides robust analgesia and can be beneficial in specific clinical settings where maintaining BP is crucial.

Pain Management:

Pain levels after surgery were evaluated at different times using the “Visual Analog Scale (VAS)”. Both groups exhibited comparable pain levels at most time points; however, significant differences were noted at 1 and 2 hours post-surgery, with Group K reporting higher pain levels. This suggests that Dexmedetomidine may provide more effective and longer-lasting analgesia in the immediate postoperative period.

1 Hour Post-Surgery: Group K had a higher “VAS score” compared to Group D (p=0.0127).

2 Hours Post-Surgery: Group K continued to report higher pain levels (p=0.0144).

Studies by Kim et al. (2013) and Song et al. (2016) have similarly highlighted the prolonged analgesic effects of Dexmedetomidine[21,36], which can be beneficial in managing acute postoperative pain and improving patient comfort. The prolonged

analgesic effect is likely due to the sedative properties of Dexmedetomidine, which enhance the overall pain control and patient comfort.

Although Ketamine did not perform as well as Dexmedetomidine in immediate postoperative pain management, it still offers considerable benefits. Ketamine's ability to provide analgesia through NMDA receptor antagonism can be especially useful in patients with chronic pain or those who are opioid-tolerant. Studies such as those by Minoshima et al. (2015) and Sardeshpande and Deshmukh (2023) have demonstrated Ketamine's efficacy in reducing postoperative opioid consumption and improving pain scores in various surgical contexts. [13,14]

Clinical Implications:

The findings have significant clinical inferences.

The use of Dexmedetomidine as an adjunct in anaesthesia protocols can enhance patient outcomes by reducing intraoperative opioid requirements and maintaining hemodynamic stability. This not only improves the safety profile of anaesthesia but also enhances postoperative recovery by minimizing opioid-related side effects and improving pain management.

Conversely, Ketamine remains a valuable tool in the anaesthesiologist’s arsenal, particularly in patients who are at a risk of hypotension, where maintaining hemodynamic stability is critical. Its ability to provide analgesia through a different mechanism than opioids can be particularly advantageous in multimodal pain management strategies.

CONCLUSION

In conclusion, our study indicates that Dexmedetomidine proves to be more effective compared to Ketamine in reducing intraoperative opioid requirements and providing hemodynamic stability in patients undergoing laparoscopic surgeries. The incorporation of Dexmedetomidine into multimodal analgesia protocols can optimize pain management, reduce opioid consumption, and improve overall patient satisfaction and safety.

SUMMARY

The present study focused on comparing two drugs, Ketamine and Dexmedetomidine, which are integral to multimodal pain management strategies.

The study aimed to examine the intraoperative opioid demand between low-dose Ketamine and Dexmedetomidine. Additionally, patients undergoing laparoscopic operations under general anaesthesia were assessed for postoperative pain, nausea, and vomiting. This randomised controlled trial involved 60 patients, “ASA grade I” and “II”, ages 18 to 60, who were treated at “KLES Prabhakar Kore Hospital & Medical Research Centre in Belagavi”. Two groups of participants were randomly assigned: Group D got an intravenous infusion of Dexmedetomidine (1 µg/kg) followed by a 0.4 µg/kg/hr infusion, and Group K received an intravenous bolus of 0.2 mg/kg followed by a 0.2 mg/kg/hr infusion. Both during and after surgery, data on hemodynamic parameters, VAS scores, and total fentanyl usage were collected.

The results indicated that there was an equal distribution of males and females in both groups. Group K had a mean age of 36.13 years, while Group D had a mean age of 47.87 years. Hemodynamic stability was better maintained in Group D, which showed a significant decrease in heart rate and more stable blood pressure readings compared to Group K, which exhibited an increase in heart rate and blood pressure. In terms of opioid requirement, Group D required significantly less Fentanyl than Group K. Postoperative pain management was more effective in Group D, which experienced lower pain levels at 1 and 2 hours post-surgery compared to Group K.

According to the study's findings, patients having laparoscopic procedures can achieve hemodynamic stability and less intraoperative opioid demand when treated with dexmedetomidine rather than ketamine.

LIMITATIONS

The current study has a few drawbacks. First, the results may not be as broadly applicable as they may be because of the limited sample size. Second, multicenter trials would be helpful to validate these results as the study was only completed at one centre. Thirdly, there was a 12-hour postoperative follow-up window, and longer-term results were not evaluated. Furthermore, variations in the patient's age and weight may have had an impact on the outcomes.

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ANNEXURE I – INFORMED CONSENT FORM

"COMPARISON BETWEEN LOW-DOSE KETAMINE & DEXMEDETOMIDINE ON INTRAOPERATIVE OPIOID REQUIREMENT IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES – A RANDOMISED CONTROL TRIAL"

Objective:

Primary objective:
To compare between Low-dose Ketamine and Dexmedetomidine in terms of effective intraoperative opioid requirement.

Secondary objective:
To compare post-operative pain and post-operative nausea & vomiting in the groups.

Introduction: Mr./Mrs. ________________________________, we are requesting you to enroll yourself in the study titled "COMPARISON BETWEEN LOW-DOSE KETAMINE & DEXMEDETOMIDINE ON INTRAOPERATIVE OPIOID REQUIREMENT IN PATIENTS UNDERGOING GENERAL ANAESTHESIA", conducted by Jawaharlal Nehru Medical College, Belagavi, under KLE University, Belagavi.

Explanation of procedure: If you agree to enroll in my study, I will ask you the present & past medical history and family history. You will be examined clinically, in detail. On the day of the surgery, you will be administered the study drugs in the intraoperative period and the hemodynamic parameters and pain will be assessed.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.
Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions: . If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

CONSENT STATEMENT

I am making a voluntary decision to participate in the study **"COMPARISON BETWEEN LOW-DOSE KETAMINE & DEXMEDETOMIDINE ON INTRAOPERATIVE OPIOID REQUIREMENT IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES – A RANDOMISED CONTROL TRIAL"**. My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE II – PROFORMA

"COMPARISON BETWEEN LOW-DOSE KETAMINE & DEXMEDETOMIDINE ON INTRAOPERATIVE OPIOID REQUIREMENT IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES – A RANDOMISED CONTROL TRIAL"

Name:	Group allotted/Sl. No.:		
Age/Sex:	Date:		
Address:	IP No.:		

GENERAL STATUS:		**DRUGS & PAST HISTORY:**
Weight:	Pulse:	
Height:	BP:	
Temp:	SpO_2:	
Pallor:		
Cyanosis:		
Clubbing:		
Pedal edema:		

CARDIORESPIRATORY SYSTEM:		
Dyspnoea:	CVS:	CNS:
Cough:	RS:	GIT:
Angina:		Endocrine:

MUSCULOSKELETAL SYSTEM:	
Teeth:	Allergy:
Jaw Movements:	Previous anaesthetic experience:
Airway assessment:	
Spine:	

INVESTIGATIONS:			
Blood group:	Blood Urea:	Total bilirubin:	CXR:
Hb:	S. Creatinine:	Direct bilirubin:	ECG:
PT:	SGPT:	Indirect bilirubin:	USG:
INR:	SGOT:	S. Albumin:	
aPTT:	FBS:		ECHO:
Platelet count:	RBS/PPBS:		
	S. Na^+:	S. Cl^-:	
	S K^+:	S. Bicarb:	

ASA Status	1	2	3	4	5	E
Pre-operative diagnosis						
Proposed surgery						
Anaesthetic procedure						

Start time of surgery:	End time of surgery:

	Heart rate	Systolic BP	Diastolic BP	MAP	Rescue analgesic?
Baseline (Before pneumoperitoneum)					
Time of initiation of pneumoperitoneum:					
5 minutes					
10 minutes					
20 minutes					
30 minutes					
60 minutes					
90 minutes					
120 minutes					
150 minutes					
180 minutes					
210 minutes					
240 minutes					

No Pain
Moderate Pain
Worst Pain
0 1 2 3 4 5 6 7 8 9 10
0 2 4 6 8 10

		VAS	HR	SBP	DBP	MAP
At PACU	**Immediate**					
	1 hour					
	2 hours					
	3 hours					
After shifting	**6 hours**					
	12 hours					

Need for any postoperative rescue analgesic -

ANNEXURE III – PHOTOGRAPHS

Photograph 1: Ketamine injection

Photograph 2: Dexmedetomidine injection

Photograph 3: Fentanyl injection

ANNEXURE IV – KEY TO MASTERCHART

ASA	American Society of Anesthesiologists
DBP	Diastolic Blood Pressure
HR	Heart Rate
hr	hour
M, F	Male, Female
MAP	Mean Arterial Pressure
mg	milligram
mins	minutes
PONV	Post Operative Nausea & Vomiting
SBP	Systolic Blood Pressure
VAS	Visual Analogue Scale

ANNEXURE V - MASTERCHART

Intraoperative period

No.	IP no.	Age	Sex	ASA	HR											SBP										
					Baseline	5 mins	10 mins	20 mins	30 mins	60 mins	90 mins	120 mins	150 mins	180 mins	210 mins	Baseline	5 mins	10 mins	20 mins	30 mins	60 mins	90 mins	120 mins	150 mins	180 mins	210 mins
1	1155659	48	F	1	100	78	80	75	80	82	74	77				110	123	106	127	110	109	110	119			
2	1163031	45	F	2	67	70	68	64	64	62	68	70	68	64	66	100	120	116	110	104	102	104	102	12	114	108
3	1162601	31	M	1	64	66	62	70	74	72	68	68	64			128	130	130	126	124	132	133	128	128		
4	1165716	56	M	1	88	82	85	83	79	81	106	89				136	134	131	118	125	142	164	134			
5	1173461	51	F	2	70	68	64	70	68	62	64	60	62			130	134	130	120	120	124	124	122	120		
6	1196636	30	F	1	80	84	82	80	76	70	68	68				106	122	119	120	107	121	135	110			
7	10072183	40	M	1	80	82	84	76	70	70	68					127	130	132	126	120	124	122				
8	1200313	60	F	2	88	90	92	88	82	84	76					144	150	150	142	140	134	130				
9	1200596	35	M	1	72	74	78	88	82	84	80					136	140	146	154	152	148	150				
10	1204130	60	M	2	100	78	80	75	80	82	74	77				110	123	106	127	110	109	110	119			
11	1201659	35	F	1	74	80	84	82	80	78	76	74				126	130	132	132	130	130	128	126			
12	1201678	57	M	2	74	80	84	82	88	78	74	72				140	150	148	152	154	146	140	136			
13	1201133	60	F	2	72	78	70	80	84	82						130	136	142	132	136	140					
14	1200793	38	F	1	74	80	82	88	84	82	74	72				124	128	130	134	128	126	110	122			
15	1201538	60	M	1	86	82	84	82	86	80						136	136	140	142	136	130					
16	1202247	36	F	1	82	80	74	72	70	76	78					120	116	120	114	120	110	124				
17	1202646	60	F	2	86	82	84	90	92	86	84	82	76	78		130	136	140	142	150	140	136	134	130	132	
18	1202554	57	M	2	74	80	84	82	88	78	74	72				140	150	148	152	154	146	140	136			
19	1203440	30	F	1	78	82	84	80	86	80	80	84				126	130	130	136	140	140	136	130			
20	1203873	57	M	1	84	90	92	88	82	78	74					150	158	160	156	148	150	142				
21	1203704	55	F	2	86	90	92	90	88	84						138	140	144	145	142	138					
22	1204130	25	M	1	62	66	62	60	64	66						120	116	124	130	128	126					
23	1203484	51	M	1	80	84	80	80	76	78	74	70	70			140	152	148	142	140	138	132	130	126		
24	1204427	20	M	1	62	66	62	64	66	70						114	120	128	124	122	126					
25	10071065	60	M	2	74	80	84	82	80	78	76	74				126	130	132	132	130	130	128	126			
26	1203907	40	F	1	90	94	86	82	84	80	77	72	74			130	138	132	128	130	126	120	128	124		
27	1203685	60	F	1	86	84	84	80	78	74	72					160	162	161	160	176	178	164				
28	1211003	30	F	1	74	78	80	76	80	84	80					126	130	134	140	132	130	140				
29	12049240	34	F	1	72	78	80	84	76	74						152	160	154	150	140	140					
30	1205035	22	F	1	66	72	70	78	78	72	68					110	116	120	124	122	120	116				
31	1205129	23	F	1	80	82	86	80	74	82	82					130	140	142	134	130	136	130				
32	1206361	29	F	1	88	90	92	94	80	82	76	76	74			144	140	138	140	130	134	132	132	130		
33	1205390	18	M	1	64	62	66	70	70	64						110	110	118	124	120	116					
34	10071056	27	M	1	78	86	90	82	80	74						117	132	135	130	132	120					
35	10008302	50	F	1	80	88	84	9	84	86	92	98	88			120	138	130	140	136	130	138	150	132		
36	10012227	38	F	1	72	78	70	80	84	82						130	136	142	132	136	140					
37	10012534	56	F	2	86	94	92	88	84	80	82					142	150	160	152	154	144	140				
38	10012598	25	F	1	76	80	82	84	74	76	72					132	136	140	134	130	130	134				
39	10014057	55	F	2	80	82	84	76	86	92	94	84	80			150	160	154	150	162	170	180	170	164		
40	10014327	30	F	2	90	84	86	84	90	92	110	106	92			100	110	114	106	110	108	122	118	112		
41	10014514	27	F	1	86	90	94	100	96	88	98					134	138	144	126	132	150	140				
42	10014603	44	F	2	82	92	86	88	94	84	96	90				130	146	140	142	136	148	138	132			
43	10015908	30	M	1	84	88	96	98	92	86	94	102	96			124	136	140	128	144	146	148	150	138		
44	10015628	32	M	1	76	84	78	90	88	86	82					126	132	142	140	130	132	130				
45	10017142	48	F	2	74	80	76	84	78	82	86					138	144	158	148	150	142	160				
46	10017281	38	F	1	80	88	86	92	94	82						140	152	160	144	162	148					
47	10017839	32	M	1	64	72	68	74	70	66	76					110	122	128	116	126	114	130				
48	10017909	44	F	2	90	94	96	98	100	92	110	102				155	156	158	160	162	164	188	170			
49	10016799	41	F	1	84	86	88	90	92	94						132	134	136	138	140	142					
50	10018463	52	F	2	90	84	82	92	94	86	88	96				140	142	144	148	146	142	150	152			
51	10017299	27	M	1	70	72	74	76	78	80						112	130	116	128	120	114					
52	10018761	29	F	1	86	80	88	78	82	90						138	130	134	126	140	128					
53	10019359	23	M	1	74	72	70	68	78	68						126	120	123	115	128	118					
54	10020630	52	F	2	88	84	82	90	78	86						155	142	148	161	144	152					
55	10020105	43	F	2	86	78	84	76	82	88	80					156	158	155	149	146	143	140				
56	10020321	42	F	1	88	90	86	84	80	82						156	159	153	149	146	142					
57	10022099	46	F	1	102	100	98	96	94	88	88	90				160	158	156	154	152	150	148	150			
58	10022272	59	F	2	82	82	82	82	80	74	86					130	136	142	140	134	130	132				
59	10022208	60	M	2	100	98	94	88	84	82						142	147	154	139	136	135					
60	10022654	57	M	2	80	84	80	80	76	78						140	152	148	142	140	138					

No.	DBP											MAP											Total Fentanyl administered (in mg)
	Baseline	5 mins	10 mins	20 mins	30 mins	60 mins	90 mins	120 mins	150 mins	180 mins	210 mins	Baseline	5 mins	10 mins	20 mins	30 mins	60 mins	90 mins	120 mins	150 mins	180 mins	210 mins	
1	68	70	81	80	77	80	72	76				82	88	89	96	88	90	85	90	0	0	0	0
2	60	70	62	64	70	70	72	68	64	60	70	73	87	80	79	81	81	83	79	47	78	83	0
3	70	74	72	72	68	70	72	72	70			89	93	91	90	87	91	92	91	89	0	0	0
4	87	79	80	75	79	85	76	86				103	97	97	89	94	104	105	102	0	0	0	25
5	70	80	78	78	72	70	82	74	70			90	98	95	92	88	88	96	90	87	0	0	0
6	74	82	76	81	82	82	105	82				85	95	90	94	90	95	115	91	0	0	0	25
7	84	82	84	76	70	70	68					98	98	100	93	87	88	86	0	0	0	0	0
8	98	100	104	90	84	82	90					113	117	119	107	103	99	103	0	0	0	0	0
9	86	90	90	94	92	96	94					103	107	109	114	112	113	113	0	0	0	0	0
10	68	70	81	80	77	80	72	76				82	88	89	96	88	90	85	90	0	0	0	0
11	80	84	86	78	78	74	70	70				95	99	101	96	95	93	89	89	0	0	0	0
12	90	94	96	92	90	90	90	86				107	113	113	112	111	109	107	103	0	0	0	0
13	80	82	90	84	70	90						97	100	107	100	92	107	0	0	0	0	0	0
14	84	80	86	84	90	88	78	80				97	96	101	101	103	101	89	94	0	0	0	0
15	90	94	90	94	80	80						105	108	107	110	99	97	0	0	0	0	0	0
16	70	74	80	76	82	84	70					87	88	93	89	95	93	88	0	0	0	0	0
17	80	84	90	86	92	90	86	80	82	80		97	101	107	105	111	107	103	98	98	97	0	0
18	90	94	96	92	94	90	90	86				107	113	113	112	114	109	107	103	0	0	0	0
19	84	90	94	92	96	80	80	80				98	103	106	107	111	100	99	97	0	0	0	0
20	90	92	90	94	90	86	84					110	114	113	115	109	107	103	0	0	0	0	0
21	86	84	90	94	86	82						103	103	108	111	105	101	0	0	0	0	0	0
22	72	80	82	78	74	80						88	92	96	95	92	95	0	0	0	0	0	0
23	90	90	88	82	84	82	80	86	82			107	111	108	102	103	101	97	101	97	0	0	0
24	70	72	74	80	76	70						85	88	92	95	91	89	0	0	0	0	0	0
25	80	84	86	78	78	74	70	70				95	99	101	96	95	93	89	89	0	0	0	0
26	90	96	98	94	90	88	84	86	80			103	110	109	105	103	101	96	100	95	0	0	0
27	100	96	84	86	84	88	78					120	118	110	111	115	118	107	0	0	0	0	0
28	84	76	80	90	94	90	84					98	94	98	107	107	103	103	0	0	0	0	0
29	90	94	96	100	90	84						111	116	115	117	107	103	0	0	0	0	0	0
30	80	84	84	90	90	80	80					90	95	96	101	101	93	92	0	0	0	0	0
31	80	90	92	84	90	82	84					97	107	109	101	103	100	99	0	0	0	0	0
32	90	92	92	90	86	84	86	80	80			108	108	107	107	101	101	101	97	97	0	0	0
33	80	82	84	80	90	76						90	91	95	95	100	89	0	0	0	0	0	0
34	65	72	74	74	70	76						82	92	94	93	91	91	0	0	0	0	0	0
35	120	138	130	140	136	130	138	150	132			120	138	130	140	136	130	138	150	132	0	0	35
36	80	82	90	84	70	90						97	100	107	100	92	107	0	0	0	0	0	0
37	80	84	92	90	92	82	84					101	106	115	111	113	103	103	0	0	0	0	0
38	80	86	86	80	74	82	84					97	103	104	98	93	98	101	0	0	0	0	0
39	90	92	86	84	80	92	110	94	92			110	115	109	106	107	118	133	119	116	0	0	30
40	60	70	68	62	70	64	76	70	62			73	83	83	77	83	79	91	86	79	0	0	27.5
41	74	80	82	76	86	84	78					94	99	103	93	101	106	99	0	0	0	0	0
42	82	94	92	84	84	86	90	88				98	111	108	103	101	107	106	103	0	0	0	0
43	72	82	76	78	84	80	82	88	74			89	100	97	95	104	102	104	109	95	0	0	33
44	74	84	80	76	86	78	88					91	100	101	97	101	96	102	0	0	0	0	0
45	90	102	106	100	92	98	104					106	116	123	116	111	113	123	0	0	0	0	0
46	94	102	100	110	96	104						109	119	120	121	118	119	0	0	0	0	0	0
47	74	84	86	76	82	88	80					86	97	100	89	97	97	97	0	0	0	0	0
48	92	94	96	98	100	102	112	108				113	115	117	119	121	123	137	129	0	0	0	33.5
49	82	84	88	86	90	92						99	101	104	103	107	109	0	0	0	0	0	0
50	92	94	96	100	98	102	104	106				108	110	112	116	114	115	119	121	0	0	0	0
51	82	78	74	80	72	82						92	95	88	96	88	93	0	0	0	0	0	0
52	72	80	74	82	78	76						94	97	94	97	99	93	0	0	0	0	0	0
53	68	70	62	66	71	63						87	87	82	82	90	81	0	0	0	0	0	0
54	88	98	108	100	105	97						110	113	121	120	118	115	0	0	0	0	0	0
55	94	88	82	84	82	88	82					115	111	106	106	103	106	101	0	0	0	0	0
56	107	105	103	100	98	96						123	123	120	116	114	111	0	0	0	0	0	0
57	99	97	93	95	93	90	87	85				119	117	114	115	113	110	107	107	0	0	0	0
58	84	82	92	90	84	90	82					99	100	109	107	101	103	99	0	0	0	0	0
59	99	96	100	98	88	86						113	113	118	112	104	102	0	0	0	0	0	0
60	90	90	88	82	84	82						107	111	108	102	103	101	0	0	0	0	0	0

Postoperative period

No.	VAS						HR						SBP						DBP						MAP						Postoperative rescue analgesic needed?	PONV
	Immediate	1 hr	2 hr	3 hr	6 hr	12 hr	Immediate	1 hr	2 hr	3 hr	6 hr	12 hr	Immediate	1 hr	2 hr	3 hr	6 hr	12 hr	Immediate	1 hr	2 hr	3 hr	6 hr	12 hr	Immediate	1 hr	2 hr	3 hr	6 hr	12 hr		
1	0	0	1	1	2	2	82	74	86	84	74	82	110	120	122	128	132	130	64	80	74	68	70	64	79	93	90	88	91	86	0	0
2	3	3	2	2	2	2	60	64	68	64	62	62	135	130	132	130	128	124	65	62	60	70	60	64	88	85	84	90	83	84	0	0
3	0	0	0	1	1	1	70	74	72	74	68	70	128	126	124	130	132	128	70	68	72	84	80	70	89	87	89	99	97	89	0	0
4	1	1	1	1	2	2	70	78	74	80	86	84	120	124	130	130	126	130	80	72	80	84	70	70	93	89	97	99	89	90	0	0
5	0	0	1	1	1	1	68	62	70	72	68	60	124	120	130	126	120	124	80	80	70	70	80	82	95	93	90	89	93	96	0	0
6	3	3	2	2	2	1	88	80	84	76	78	76	116	122	110	108	120	120	72	84	69	70	80	70	87	97	83	83	93	87	0	0
7	3	2	2	1	1	1	86	82	80	78	74	76	130	130	128	124	130	130	90	80	78	68	84	90	103	97	95	87	99	103	0	0
8	2	1	1	1	1	1	84	80	80	86	82	80	140	138	130	140	140	140	100	90	90	80	90	90	113	106	103	100	107	107	0	0
9	2	1	1	1	1	1	82	84	76	80	82	80	140	138	140	136	140	140	90	72	78	74	90	88	107	94	99	95	107	105	0	0
10	0	0	1	1	2	2	82	74	86	84	74	82	110	120	122	128	132	130	64	80	74	68	70	64	79	93	90	88	91	86	0	0
11	0	0	0	1	1	1	82	78	72	74	70	82	128	130	126	124	130	130	80	80	76	70	80	76	96	97	93	88	97	94	0	0
12	0	0	0	0	1	1	80	82	80	76	84	82	140	140	136	140	138	140	88	90	74	78	72	90	105	107	95	99	94	107	0	0
13	0	1	1	1	1	1	80	82	78	74	82	84	144	136	130	132	130	132	92	84	80	84	70	68	109	101	97	100	90	89	0	0
14	0	0	0	0	1	1	74	80	82	80	76	72	130	110	120	122	120	120	80	72	7	64	78	84	97	85	45	83	92	96	0	0
15	0	0	0	1	2	2	82	80	80	76	78	80	130	132	130	130	132	130	86	82	70	80	74	76	101	99	90	97	93	94	0	0
16	0	1	1	2	3	3	80	78	80	74	72	80	128	126	124	128	130	128	80	72	80	76	80	80	96	90	95	93	97	96	0	0
17	0	1	2	3	3	3	84	80	78	82	84	80	136	138	130	136	128	126	80	74	82	76	70	68	99	95	98	96	89	87	0	0
18	0	0	0	1	2	3	80	82	80	76	84	82	140	140	136	140	138	140	88	90	74	78	72	90	105	107	95	99	94	107	0	0
19	0	2	3	3	3	3	80	82	80	78	84	82	132	136	128	132	136	132	76	70	74	80	76	70	95	92	92	97	96	91	0	0
20	0	0	0	0	0	1	80	74	76	72	80	76	140	135	134	142	143	140	90	86	90	82	87	80	107	102	105	102	106	100	0	0
21	0	0	0	0	1	1	86	82	80	80	82	80	135	132	130	142	140	136	76	84	80	78	80	74	96	100	97	99	100	95	0	0
22	0	0	0	0	2	3	70	68	64	66	70	72	130	128	120	128	130	130	80	74	76	72	70	80	97	92	91	91	90	97	0	0
23	0	0	0	2	3	3	76	80	82	80	74	80	130	132	140	143	128	140	84	70	80	76	90	90	99	91	100	98	103	107	0	0
24	0	0	0	0	0	1	66	62	70	74	70	72	130	126	120	124	128	130	80	74	78	80	70	80	97	91	92	95	89	97	0	0
25	0	0	0	1	1	1	82	78	72	74	70	82	128	130	126	124	130	130	80	80	76	70	80	76	96	97	93	88	97	94	0	0
26	0	0	2	2	2	3	86	80	78	74	76	80	130	134	140	130	128	124	86	82	80	80	78	76	101	99	100	97	95	92	0	0
27	0	0	0	2	2	2	82	78	84	86	82	76	150	150	152	148	150	150	90	86	84	86	92	86	110	107	107	107	111	107	0	0
28	0	1	2	2	2	2	80	84	82	80	86	84	136	132	124	120	126	122	76	80	72	80	84	74	96	97	89	93	98	90	0	0
29	0	0	0	0	0	1	76	70	74	70	80	78	140	136	140	140	138	140	80	84	70	72	72	80	100	101	93	95	94	100	0	0
30	0	0	0	0	1	1	70	64	68	62	70	74	120	114	110	120	122	110	70	74	80	80	80	74	87	87	90	93	94	86	0	0
31	0	0	0	0	2	2	84	80	80	72	84	84	140	138	130	130	130	134	90	72	80	70	70	72	107	94	97	90	90	93	0	0
32	0	0	0	1	1	2	86	80	80	74	80	84	138	130	130	134	128	128	78	78	70	74	70	70	98	95	90	94	89	89	0	0
33	0	1	1	1	1	1	70	72	64	60	62	62	110	114	110	118	120	120	74	74	80	72	80	84	86	87	90	87	93	96	0	0
34	0	1	1	1	1	1	84	80	80	74	82	80	130	128	120	120	130	124	70	70	74	70	72		90	89	89	87	91	41	0	0
35	0	0	1	1	2	2	90	88	86	73	74	72	130	126	130	128	120	130	90	82	86	70	90	80	103	97	101	89	100	97	0	0
36	0	1	1	1	2	1	80	82	78	74	82	84	144	136	130	132	130	132	92	84	80	84	70	68	109	101	97	100	90	89	0	0
37	1	1	1	1	3	3	80	82	76	80	74	72	142	140	140	140	144	140	80	82	70	90	84	92	101	101	93	107	104	108	0	0
38	2	2	2	3	3	3	84	82	80	74	78	80	140	142	140	138	132	134	90	86	92	76	80	80	107	105	108	97	97	98	0	0
39	2	2	2	2	2	2	86	84	82	86	80	78	160	162	170	136	160	156	84	92	90	84	82	80	109	115	117	101	108	105	0	0
40	2	3	3	3	2	2	94	90	92	90	100	88	110	100	104	100	112	100	70	68	62	60	68	64	83	79	76	73	83	76	0	0
41	1	1	2	2	2	2	96	98	90	94	88	100	138	142	144	132	126	140	78	80	86	82	76	84	98	101	105	99	93	103	0	0
42	3	3	3	2	2	2	82	96	88	94	92	84	150	140	142	138	140	136	96	88	82	84	90	80	114	105	102	102	107	99	0	0
43	1	1	1	2	2	2	98	86	88	94	92	96	140	130	138	126	124	126	86	76	84	78	80	72	104	94	102	94	95	90	0	0
44	1	1	1	1	1	2	80	76	90	88	84	80	140	136	130	134	142	132	82	86	74	80	84	88	101	103	93	98	103	103	0	0
45	1	1	2	2	2	2	88	74	84	82	86	88	146	140	154	160	152	144	94	108	96	94	100	92	111	119	115	116	117	109	0	0
46	1	1	1	1	1	1	90	96	84	82	88	94	156	164	158	142	150	166	106	112	98	108	94	106	123	129	118	119	113	126	0	0
47	1	2	2	2	2	2	64	70	68	74	72	76	118	120	124	112	130	126	84	86	78	76	88	82	95	97	93	88	102	97	0	0
48	3	3	2	2	2	2	104	98	96	100	92	90	172	162	156	150	152	154	94	96	98	94	96	92	120	118	117	113	115	113	0	0
49	2	1	1	1	1	1	96	84	90	86	94	92	144	146	148	150	152	154	94	84	88	90	92	94	111	105	108	110	112	114	0	0
50	3	2	2	2	1	1	94	92	90	88	86	84	154	156	150	148	144	142	108	102	98	94	102	100	123	120	115	112	116	114	0	0
51	1	1	1	1	1	1	82	84	72	74	76	78	126	118	124	122	130	124	76	82	70	82	72	78	93	94	88	95	91	93	0	0
52	2	2	2	2	2	2	84	86	88	80	84	82	142	122	132	124	136	120	82	70	82	74	80	72	102	87	99	91	99	88	0	0
53	3	2	2	2	2	1	70	76	68	72	74	66	130	112	127	121	113	129	69	65	70	61	67	64	89	81	89	81	82	86	0	0
54	3	3	3	2	1	1	92	80	84	88	82	90	163	150	158	143	140	148	110	102	107	96	104	102	128	118	124	112	116	117	0	0
55	1	1	1	1	1	0	86	78	84	76	82	88	155	150	148	152	156	150	96	94	90	88	92	84	116	113	109	109	113	106	0	0
56	1	1	1	1	2	2	84	86	88	78	80	90	135	130	142	150	158	144	88	83	80	90	92	94	104	99	101	110	114	111	0	0
57	1	1	1	0	0	0	90	88	96	92	82	90	152	148	142	140	138	132	87	92	90	84	86	90	109	111	107	103	103	104	0	0
58	2	1	1	1	1	0	84	80	80	72	84	84	140	138	130	130	130	134	90	72	80	77	70	72	107	94	97	95	90	93	0	0
59	1	1	1	1	1	1	88	92	84	86	82	78	148	150	144	142	140	146	98	96	92	90	94	94	115	114	109	107	109	111	0	0
60	0	0	0	1	1	1	74	70	70	76	82	80	132	130	126	130	132	143	80	86	82	84	70	76	97	101	97	99	91	98	0	0