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Original Research Article

Preoperative Intravenous Dexmedetomidine for Reducing Postoperative Pain Scores and Opioid Use in Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

Background: Laparoscopic cholecystectomy is minimally invasive, but early postoperative shoulder pain (visceral, incisional, and referred) is common and often requires opioid use. Dexmedetomidine has sympatholytic, sedative and analgesic sparing properties without clinically significant respiratory depression. Dexmedetomidine is an alpha-2 adrenergic agonist that has been shown to decrease postoperative pain and the need for opioids in various surgical settings. The authors sought to determine if a single preoperative intravenous dose of dexmedetomidine would affect postoperative opioid use and pain scores after elective laparoscopic cholecystectomy.

Method: The study design was a prospective, randomized, double-blind, placebo controlled trial of 80 adults with American Society of Anesthesiologists (ASA) physical status I–II who were randomly assigned to either receive dexmedetomidine 0.5 µg/kg (Group D, n=40) or volume-matched normal saline (Group C, n=40) over 10 minutes prior to general anesthesia induction. Standard anesthesia, multimodal analgesia during surgery and postoperative morphine PCA was used in all patients. The main outcome was total morphine use at 24 hours. Secondary outcomes were numerical rating scale pain scores, time to first analgesic demand, intraoperative use of fentanyl, postoperative nausea and vomiting, sedation, and hemodynamic adverse events.

Results: The 24-hour morphine consumption was significantly lower in Group D compared to Group C (12.6±4.3 mg versus 19.8±5.6 mg; mean difference −7.2 mg, 95% CI −9.4 to −5.0; $p<0.001$). Resting pain scores were lower at 1, 2, 4 and 6 hours, and movement-evoked pain was lower at 12 hours. Time to first analgesic demand was prolonged (78.4±22.1 versus 34.6±15.7 minutes; $p<0.001$), and intraoperative fentanyl use was reduced (108±29 versus 154±36 µg; $p<0.001$). The incidence of postoperative nausea and vomiting was 15.0% and 35.0% respectively ($p=0.039$). Transient bradycardia occurred more often with dexmedetomidine, but was treated routinely.

Conclusion: Clinically significant opioid sparing and better early pain control were achieved with pre-operative dexmedetomidine 0.5 µg/kg in laparoscopic cholecystectomy with no significant adverse effects.

Keywords: Dexmedetomidine; Laparoscopic Cholecystectomy; Postoperative Pain; Opioid Consumption; Multimodal Analgesia; Anesthesia.

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Introduction

For the majority of patients with symptomatic gallbladder disease, laparoscopic cholecystectomy is performed rather than open cholecystectomy, due to the advantages of smaller incisions, earlier mobilization and shorter hospital stays. However, postoperative pain is clinically relevant and occurs due to multiple mechanisms such as pain from the site of the trocar, parietal peritoneal irritation, visceral nociception, residual carbon dioxide, irritation of the diaphragm, and inflammatory sensitization. It is most intense in the first few hours after surgery, and if not properly managed, can cause a delay in ambulation and/or discharge. Therefore, procedure specific reviews will support scheduled non-opioid analgesics and opioids will only be used for breakthrough pain [1]. Today, the pain management of the postoperative patient is based on multimodal treatment, which involves the use of complementary mechanisms and drugs, while reducing the occurrence of nausea, vomiting, sedation, respiratory depression, ileus, urinary retention and delayed functional recovery

associated with the use of opioids [2]. Opioid-sparing strategies are also aligned with enhanced-recovery principles, in which the use of anesthetic technique and effective analgesia are combined to minimize the physiological impact of surgery and promote early recovery [3].

Dexmedetomidine is a very selective alpha-2 adrenergic receptor agonist. Central presynaptic alpha-2 receptor activation results in reduced norepinephrine release; activation of alpha-2 receptors in the locus coeruleus and spinal dorsal horn leads to sedation, anxiolysis, sympatholysis and antinociception. The pharmacokinetic and pharmacodynamic properties allow bolus doses before induction or infusion, but the dose and infusion rate affect bradycardia and hypotension [4]. Dexmedetomidine tends to leave ventilatory drive intact at clinically relevant doses, which is advantageous as an adjunctive agent in ambulatory and short-stay anesthesia [5].

In surgical populations, dexmedetomidine has been linked to decreased postoperative pain intensity and opioid consumption, but the direct extrapolation of this is limited by inter-study differences in dose, time, background analgesics, and surgical procedure [6]. In a meta-analysis, limited to laparoscopic cholecystectomy, opioid use was found to be reduced, duration of analgesics was longer, and there was less postoperative nausea and vomiting, but the trials were small and had different opioid regimens [7].

There have been conflicting results in individual laparoscopic cholecystectomy trials. Park et al. reported only a short-term decrease in early pain with the use of dexmedetomidine in multimodal analgesia [8] and Bielka et al. showed reduced consumption of morphine and a prolonged time to rescue analgesia during a perioperative infusion [9]. Pre-induction dexmedetomidine was found to improve hemodynamic stability, recovery characteristics and postoperative pain by Ye et al. [10]. More recently, a double blind study of low dose intravenous premedication showed better early pain and peri-operative stability, but further controlled studies with standardised measurement of postoperative opioid are appropriate [11].

The aim of the present study was to evaluate if a single preoperative intravenous dose of dexmedetomidine 0.5 μg/kg decreases cumulative postoperative morphine use and numerical rating scale (NRS) pain scores in the first 24 hours after elective laparoscopic cholecystectomy.

We hypothesized that dexmedetomidine would reduce opioid requirement, facilitate early pain control and minimize opioid-related adverse effects without causing clinically significant hemodynamic instability.

Materials and Methods

Design and setting of the study. This was a prospective, randomized, double blind and placebo controlled parallel group study conducted in a tertiary care teaching hospital for a period of 12 months in adult patients undergoing elective laparoscopic cholecystectomy.

Participants. The patients were eligible if they were aged 18–60 years, of either sex, with American Society of Anesthesiologists physical status I or II, and were undergoing a three- or four-port laparoscopic cholecystectomy under general anesthesia. Patients were excluded if they refused to participate, were pregnant or lactating, had a body mass index >35 kg/m², an anticipated difficult airway, a resting heart rate <55 beats per minute, second or third degree heart block, uncontrolled hypertension, clinically important cardiac, hepatic, renal, neurological, or psychiatric disease, chronic opioid or sedative use, current beta blocker or alpha-2 agonist therapy, allergy to study drugs, conversion to open surgery, operative time >120 minutes, or inability to use the numerical rating scale or patient-controlled analgesia device.

Sample size. The sample size was determined for the primary endpoint of 24 hours of morphine use. With a clinically relevant 30% reduction, two-sided alpha of 0.05 and power of 80%, 34 patients per group were needed assuming a control mean of 18 mg and a control SD of 7 mg. To account for the exclusions and incomplete follow-up, 40 participants were enrolled in each group.

Randomization and blinding. A random sequence of variable block sizes was prepared by an investigator who was not involved in patient care or outcome assessment using a computer-generated sequence. The allocation was hidden in numbered envelopes that were opaque. Twenty mL syringes of either dexmedetomidine 0.5 μg/kg in normal saline or 20 mL of normal saline were prepared by a pharmacist or anesthesiologist who was not involved in the data collection. Patients, attending anesthesiologists, surgeons, post-anesthesia care unit staff and outcome assessors were blinded to allocation.

Intervention/Anesthesia protocol. Standard fasting was performed and transferred to the operating room where electrocardiography, non-invasive blood pressure, pulse oximetry, capnography, temperature and neuromuscular monitoring were applied. Group D was given dexmedetomidine 0.5 μg/kg over 10 minutes, and Group C was given volume-matched saline at the same rate, which was completed around 5 minutes before induction. Induction of general anesthesia was achieved using fentanyl 2 μg/kg, propofol 1.5–2.5 mg/kg and atracurium 0.5 mg/kg; sevoflurane was used in an

oxygen-air mixture to maintain a BIS of 40–60. Ventilation was controlled for an end-tidal CO2 level of 35-40 mmHg. The pneumoperitoneum pressure was kept at 12–14 mmHg.

Analgesia around the operation and rescue therapy. Before surgery, all patients were given 1 g of paracetamol and 75 mg of diclofenac intravenously (unless contraindicated). Fentanyl 0.5 µg/kg was given if there was an increase in heart rate or mean arterial pressure of more than 20% above the baseline level, despite the depth of the anaesthetic. The port sites were infiltrated with 0.25% bupivacaine at the time of skin closure. Reversal of neuromuscular blockade was achieved with neostigmine and glycopyrrolate and extubation was done once the standard criteria were met. All patients were given paracetamol 1 g every 6 hours and morphine PCA (1 mg bolus, 10-minute lockout and no background infusion) postoperatively. Ondansetron 4 mg was given intravenously for nausea or vomiting.

Outcome measures. The main outcome was the total amount of morphine used in the first 24 hours after surgery. Secondary outcomes included the amount of fentanyl used during surgery, the time it took for patients to request their first dose of PCA, pain at rest and during movement or coughing (using an 11-point numerical rating scale from 0 = no pain to 10 = worst imaginable pain) at 1, 2, 4, 6, 12, and 24 hours after surgery, postoperative nausea and vomiting, rescue antiemetic use, sedation, bradycardia, hypotension, respiratory depression, time to extubation, and post-anesthesia care unit stay. Bradycardia was considered to be heart rate < 50 beats/min and was treated with atropine if persistent or symptomatic. Hypotension was considered to be mean arterial pressure < 65 mmHg or > 20% below baseline and was treated with fluids and mephentermine as needed. Respiratory depression was considered as respiratory rate < 8/min or oxygen saturation < 92% that needed intervention.

Statistical analysis. IBM SPSS Statistics 27 was used for data analysis. Continuous variables were tested for normality, and then presented as mean ± SD or median (IQR). Independent-samples t test or Mann–Whitney U test was used for between-group comparisons. The chi-square test or Fisher exact test was used for comparing categorical variables. A mixed-effects model was used to analyze repeated pain measurements with group, time and group-by-time interaction as fixed effects. The mean differences with 95% confidence intervals were reported. Two-sided p value < 0.05 was defined as statistically significant.

Results

Eighty-six patients were assessed for eligibility. Six were excluded before randomization: three did not meet inclusion criteria, two declined participation, and one had a predicted difficult airway. Eighty patients were randomized equally, received the allocated intervention, completed 24-hour follow-up, and were included in the analysis. Baseline demographic and perioperative characteristics were comparable between groups (Table 1). Cumulative morphine use at 24 hours, the primary outcome, was 12.6±4.3 mg in Group D and 19.8±5.6 mg in Group C, corresponding to a mean reduction of 7.2 mg (95% CI 5.0–9.4 mg; p<0.001). Dexmedetomidine also reduced intraoperative fentanyl requirement and prolonged the time to first postoperative analgesic demand. Resting and movement-evoked pain scores were lower during the early postoperative period, with the largest differences observed at 1–4 hours (Table 2). The group-by-time interaction for resting pain was significant (p<0.001).

Postoperative nausea and vomiting occurred less frequently in Group D. Transient bradycardia was numerically more common after dexmedetomidine, but the difference was not statistically significant and all episodes responded to dose completion, observation, or a single dose of atropine. No patient experienced respiratory depression, severe hypotension, delayed emergence requiring ventilation, or unplanned intensive care admission. Recovery outcomes and adverse events are summarized in Table 3.

Table 1: Baseline demographic and perioperative characteristics

Variable	Group D (n=40)	Group C (n=40)	p value
Age (years)	41.7±10.4	42.9±9.8	0.598
Female sex, n (%)	29 (72.5)	30 (75.0)	0.799
Body mass index (kg/m²)	25.8±3.2	26.1±3.5	0.690
ASA I/II, n	24/16	22/18	0.653
Duration of surgery (min)	58.6±13.4	60.9±14.1	0.458
Duration of anesthesia (min)	78.2±14.8	80.6±15.3	0.477
Baseline heart rate (beats/min)	78.3±9.1	79.7±8.7	0.485
Baseline mean arterial pressure (mmHg)	94.2±8.5	95.1±9.0	0.647

Values are mean±standard deviation unless otherwise stated. ASA, American Society of Anesthesiologists.

Table 2: Opioid consumption and postoperative pain outcomes

Variable	Group D (n=40)	Group C (n=40)	p value
Intraoperative fentanyl (μg)	108±29	154±36	<0.001
Time to first PCA demand (min)	78.4±22.1	34.6±15.7	<0.001
Morphine consumption, 6 h (mg)	5.1±2.2	9.0±3.1	<0.001
Morphine consumption, 12 h (mg)	8.4±3.1	13.9±4.2	<0.001
Morphine consumption, 24 h (mg)	12.6±4.3	19.8±5.6	<0.001
NRS at rest, 1 h	3.1±1.0	4.4±1.2	<0.001
NRS at rest, 2 h	2.8±0.9	4.0±1.1	<0.001
NRS at rest, 4 h	2.5±0.8	3.5±1.0	<0.001
NRS at rest, 6 h	2.3±0.8	3.0±0.9	0.001
NRS at rest, 12 h	2.0±0.7	2.3±0.8	0.079
NRS at rest, 24 h	1.6±0.6	1.8±0.7	0.173
NRS with movement, 6 h	3.4±0.9	4.3±1.1	<0.001
NRS with movement, 12 h	2.9±0.8	3.5±0.9	0.003
NRS with movement, 24 h	2.3±0.7	2.6±0.8	0.079

Values are mean±standard deviation. PCA, patient-controlled analgesia; NRS, numerical rating scale.

Table 3: Recovery characteristics and adverse events

Variable	Group D (n=40)	Group C (n=40)	p value
Time to extubation (min)	9.8±3.1	9.1±2.8	0.293
PACU stay (min)	46.5±10.8	49.7±12.1	0.216
PONV, n (%)	6 (15.0)	14 (35.0)	0.039
Rescue ondansetron, n (%)	5 (12.5)	12 (30.0)	0.056
Bradycardia, n (%)	5 (12.5)	1 (2.5)	0.201
Hypotension, n (%)	4 (10.0)	2 (5.0)	0.675
Sedation score ≥3 in PACU, n (%)	7 (17.5)	2 (5.0)	0.154
Respiratory depression, n (%)	0	0	—
Unplanned admission, n (%)	0	0	—

PACU, post-anesthesia care unit; PONV, postoperative nausea and vomiting.

Discussion

The main result of this randomized trial was that the single-dose of dexmedetomidine 0.5 μg/kg before surgery resulted in a reduction of 24-hour morphine usage of about 36% following laparoscopic cholecystectomy. The intervention also reduced the time to the first analgesic demand, reduced intraoperative fentanyl use and improved pain scores during the most intense period of postoperative pain. The effects were realized without respiratory depression or prolonged recovery, but were more likely to be associated with transient bradycardia in the dexmedetomidine group.

The clinical significance of opioid sparing for a short-stay procedure in which opioid side effects could affect oral intake, mobilization and discharge is clinically significant. Chilkoti et al. found that a low-dose infusion of dexmedetomidine started prior to induction decreased early pain and 24-hour analgesic requirement and dampened pneumoperitoneum-induced hemodynamic responses [12]. Another randomized trial comparing intravenous and intraperitoneal dexmedetomidine also revealed that 0.5 μg/kg of intravenous dexmedetomidine was effective for postoperative analgesia [13]. The present design is unique in that it allows for a single pre-induction systemic dose to be isolated and standardized morphine patient-controlled analgesia (PCA) is used, which provides an objective measure of opioid demand. The decrease in pain was most noticeable in the first 6 postoperative hours, and was less by 12–24 hours. This time course is consistent with the pharmacology. Dexmedetomidine reduces central sympathetic activity and spinal nociceptive transmission during and immediately after surgery, and may reduce acute opioid tolerance or hyperalgesia with reduced opioid exposure during surgery. The results also support a randomized study that showed that dexmedetomidine resulted in prolonged analgesia and reduced pain scores compared with intravenous paracetamol [14]. The convergence of pain scores at later time points, however, suggests that dexmedetomidine is a part of multimodal analgesia and should not be used as a substitute for scheduled Paracetamol, non-steroidal anti-inflammatory drugs and local anesthetic infiltration. The incidence of postoperative nausea and vomiting was lower with dexmedetomidine. This effect is likely indirect, due to decreased peri-operative opioid exposure, and is likely also due to sympatholysis and decreased volatile anesthetic requirements. Bakri et al. reported that dexmedetomidine also decreased the amount of pain medication and postoperative pain, and had comparable antiemetic effects to

dexamethasone following laparoscopic cholecystectomy [15]. The absolute difference in postoperative nausea and vomiting was 20% in the present data set, which may be a clinically meaningful difference in recovery in patients at high risk for postoperative nausea and vomiting. The main safety concern was bradycardia. Alpha-2 agonism reduces central sympathetic outflow and may increase vagal predominance, especially if administered as a loading dose, in patients with low resting heart rate, or in those who are taking beta-blockers. A meta-analysis of the effects of preoperative dexmedetomidine in laparoscopic cholecystectomy showed that there was an increased risk of intraoperative bradycardia, and that anesthetic and opioid requirements were reduced [16]. More general evidence from laparoscopy also indicates reduced nausea, vomiting and shivering, but highlights the importance of hemodynamic monitoring [17]. In our protocol, patients with baseline bradycardia or conduction disease were excluded and the 0.5 μg/kg dose was infused over 10 minutes. The episodes observed were short-lived and easily treated, but routine use should be individualized.

The findings also support the growing interest in opioid minimizing and opioid-free anesthesia. Bakan et al. demonstrated that total intravenous anesthesia with dexmedetomidine and lidocaine might decrease the amount of fentanyl required in the postoperative period and postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy [18]. Another randomized study that combined dexmedetomidine with ketamine reported decreased early rescue analgesia and less postoperative nausea and vomiting [19]. These multidrug regimens may be beneficial for certain patients, but can be challenging to determine the contribution and toxicity of each drug.

In contrast, the current study indicates that a small dose of dexmedetomidine prior to surgery can lead to a measurable reduction in opioid use without compromising a standard balanced-anesthesia technique. There is also more recent prospective evidence examining the use of dexmedetomidine as an anesthetic adjuvant other than for pain outcomes. Silva et al. reported good clinical and inflammatory results in the perioperative period in videolaparoscopic cholecystectomy [20]. In addition to the current data, these data would benefit further trials that incorporate patient-centered recovery outcomes, including quality-of-recovery scores, readiness for discharge, sleep quality, and persistent postsurgical pain. Higher loading doses or longer infusion durations may lead to a greater degree of bradycardia and sedation, but not necessarily to a greater degree of analgesia, hence dose-response studies are of particular importance.

There are some limitations to this study. First, it is a single-center protocol in relatively healthy adults with uncomplicated elective surgery; these findings may not be applicable to older patients, emergency cholecystectomy, severe cardiopulmonary disease, or longer procedures. Second, numerical rating scales do not adequately reflect functional interference, shoulder pain, or patient satisfaction, which are all components of pain. Third, the study was designed to detect changes in morphine use and not rare side effects. Fourth, clinically, the depth of anesthesia and nociception were standardized but plasma drug levels were not measured. Lastly, follow-up was limited to 24 hours, which did not allow for evaluation of chronic pain or opioid use after discharge.

Nevertheless, there are practical advantages to the design: concealed randomization, double blinding, standardized anesthetic and analgesic protocol, objective patient-controlled morphine measurement, repeated pain assessment, and systematic monitoring for hemodynamic and opioid-related adverse events. The results provide evidence for the potential of using dexmedetomidine before surgery as a valuable tool for achieving early effective analgesia and minimizing opioid exposure, provided that the patient is appropriately selected and closely monitored.

Conclusion

Dexmedetomidine 0.5 μg/kg IV preoperatively reduced 24-hour morphine consumption, decreased intraoperative fentanyl requirement, prolonged the time to first analgesic demand and improved early postoperative pain scores after LC. It also reduced postoperative nausea and vomiting, without delaying extubation or post-anesthetic care unit discharge. Transient bradycardia still is a monitoring concern. Dexmedetomidine may therefore be used as a clinically useful opioid-sparing adjunct in a well-designed multimodal approach to the management of pain in the appropriate patient.

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