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Effects of perioperative infusion of lidocaine versus dexmedetomidine on postoperative pain and recovery in patients undergoing laparoscopic cholecystectomy: A randomized trial

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Abstract
Background: It is important to have good postoperative pain control and early recovery after laparoscopic cholecystectomy (LC). Intravenous lidocaine has anti-hyperalgesic, anti-inflammatory and analgesic effects while dexmedetomidine provides anti-nociception, analgesic, sedative and sympatholytic effects. Both these drugs can be used as adjuvants to improve recovery after LC.
Aim: To evaluate the effects of perioperative infusion of lidocaine versus dexmedetomidine in patients undergoing LC with regards to: postoperative pain scores, analgesic consumption and recovery profile.
Methods: Eighty patients of either sex, aged 20-60 years, ASA I and II undergoing LC were randomly allocated to Group L and Group D. In Group L, patients received intravenous lidocaine 1.5 mg kg^{-1} followed by an infusion of 2 mg kg^{-1} hr^{-1} and in Group D, patients were given 1 µg kg^{-1} dexmedetomidine followed by an infusion of 0.4 µg kg^{-1} hr^{-1}. Postoperative sedation score, pain scores and analgesic consumption and quality of recovery were assessed.
Results: Postoperative sedation score, requirement of additional postoperative analgesia, nausea, vomiting and requirement of anti-emetics and the mean VAS score over 24 hours were comparable in both the groups. The time taken to achieve PADSS score ≥ 9 was 33.17 ± 6.27 mins in Group D versus 39.75 ± 11.17 mins in Group L (p=0.02). The combined QoR score was 199 ± 0.92 in Group D versus 196.65 ± 2.16 in Group L (p=0.0001).
Conclusion: Perioperative infusions of lidocaine and dexmedetomidine were effective and safe adjuvants to improve recovery after LC. However, the postoperative recovery profile was better with dexmedetomidine infusion and it may be considered the superior adjuvant in outpatient laparoscopic surgery.

Keywords: Laparoscopic cholecystectomy, postoperative pain, quality of recovery, dexmedetomidine, lidocaine

Introduction

Postoperative recovery is a complex process consisting of various outcomes, such as pain, physiological endpoints, incidence of adverse events and changes in psychological status. Multimodal analgesia has been proposed for pain relief and reduction of opioid related side effects. However, quality of recovery depends on other factors, like nausea and vomiting, duration of ileus, attainment of physical independence and comfort, early ambulation etc.

Systemic lidocaine is an effective adjunct to reduce postoperative pain, nausea and vomiting and the duration of ileus and hospital stay [1, 2, 3, 4]. It is suggested that lidocaine provides a true preventive analgesia by preventing induction of central hyperalgesia and leading to an improvement in the quality of postoperative recovery. Dexmedetomidine is a highly selective α-2 adrenoceptor agonist that provides sedation, analgesia and sympatholysis. Perioperative administration promotes haemodynamic stability and leads to lesser postoperative analgesic consumption, nausea, vomiting and respiratory depression, facilitating an earlier postoperative recovery [5].

The Global QoR-40 questionnaire has been used to evaluate the QoR (Quality of Recovery). [6] A multitude of studies show that intravenous lidocaine enhances the QoR after laparoscopic cholecystectomy. Dexmedetomidine provides haemodynamic stability and has analgesic and anaesthetic sparing properties. Several studies have summarised that improved postoperative recovery is due to a lowering of opioid consumption.

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Keeping this in mind we hypothesised that dexmedetomidine may provide a superior quality of recovery during laparoscopic surgeries and decided to evaluate the effects of intraoperative intravenous infusions of lidocaine and dexmedetomidine in reducing postoperative pain and improving the recovery profile in patients undergoing laparoscopic cholecystectomy using the Global QoR-40 questionnaire.

Methods

Ethical approval was provided by the hospital ethical committee. This double- blind randomized controlled study was conducted from March 2016 to March 2017 on 80 adult patients of either sex, aged 20-60 years, ASA physical status I and II, undergoing laparoscopic cholecystectomy under general anaesthesia. Tufanogullari and colleagues [7] studied the reductions in anesthetic and analgesic requirements after dexmedetomidine infusion in patients undergoing bariatric surgery. Assuming that the use of dexmedetomidine and magnesium infusions should cause similar reductions in postoperative analgesic requirements in patients undergoing laparoscopic cholecystectomy, a sample size of 35 patients in each group was calculated for achieving a power of study equal to 80% and a p- value of 0.05 with mean VAS score over 24 hour being the primary outcome variable. We recruited 40 patients in either group. Written informed consent was obtained. Patients with history of allergy to study drug, chronic use of analgesics or any chronic drug therapy, alcohol abuse, obesity, decreased autonomic control (diabetes, chronic hypertension, severe cardiac disease, β-blocker or calcium channel blocker therapy), renal or hepatic insufficiency and pregnant patients were excluded from the study.

During the pre-operative visit, patients were familiarized with use of a 10-point visual analogue scale (VAS), where 0 corresponds to no pain and 10 corresponds to the worst pain imaginable and the QoR questionnaire. Patients were randomly allocated to Group L (Lidocaine) or Group D (Dexmedetomidine) by computer-generated random number tables and group assignments were sealed in sequentially numbered opaque envelopes, which were opened immediately before surgery. Patients were blinded to their group allocation.

On arrival of the patient in the operation theatre, intravenous access and standard non-invasive monitoring was established and all patients received 1 mg intravenous midazolam. Five minutes later all patients in both groups received the study drug. In Group L, patients received intravenous lidocaine 1.5 mg kg^{-1} followed by an infusion of 2 mg kg^{-1} hr^{-1} and in Group D, patients were given 1 μg kg^{-1} dexmedetomidine followed by an infusion 0.4 μg kg^{-1}hr^{-1}. In both groups, bolus dose of the study drug was prepared in a volume of 20 ml and infused over 10 minutes and the hourly infusion rate was prepared in a volume of 50 ml to be infused over 1 hour. All the study medications were prepared by an independent investigator and all observations made by another investigator who was blinded to the study drug.

General anaesthesia was then induced with fentanyl 1.5 μg kg^{-1} and propofol 1-2 mg kg^{-1}. Rocuronium 0.6 mg kg^{-1} was administered for neuromuscular blockade and the airway was secured by an appropriate sized cuffed endotracheal tube. Maintenance of anaesthesia in both groups was by 66% N_2O in O_2, isoflurane and intermittent rocuronium. The

patient's lungs were mechanically ventilated to maintain normocarbia. Fifteen minutes before the end of surgery, all patients received ketorolac 30 mg and ondansetron 0.1 mg kg^{-1}. Infusion of the study drug was discontinued on removal of trocars. Neuromuscular blockade was reversed with neostigmine and glycopyrrolate. Patients were shifted to Post Anaesthesia Care Unit (PACU).

Immediately on arrival in the PACU, sedation was assessed by sedation score [8] as 1-awake, 2-sleepy but arousable and 3-sleepy difficult to awake. All the patients were kept in the PACU for 24 hours and pain was assessed at 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, and 24 hr postoperatively using the VAS score. When the VAS score was $\geq$3 or when the patient requested analgesia, intravenous diclofenac 1.5 mg kg^{-1} was administered. Any patient who complained of pain < 8 hours after diclofenac was given 50 mg intravenous tramadol. If the patient complained of pain > 8 hours after diclofenac, a repeat dose of 1.5 mg kg^{-1} diclofenac was to be administered. The total postoperative analgesic consumption over 24 hours was recorded. Any incidence of postoperative nausea and/or vomiting was recorded and if required, intravenous metoclopramide 10 mg was given, followed by ondansetron 0.1 mg kg^{-1}, if necessary. The Modified Post Anaesthesia Discharge Scoring System (PADSS) score was recorded every 15 minutes until the patient reached PADSS score $\geq$ 9. PADSS assesses 5 criteria: vital signs, ambulation, pain, nausea and/or vomiting, and surgical bleed. Each criterion was scored on 0-2 scale and the time taken to achieve a PADSS score $\geq$ 9 was noted. Twenty-four hours later, patients were asked questions as per the Quality of Recovery-40 (QoR-40) questionnaire and the QoR score was recorded. The questionnaire consists of 40 questions that examine 5 domains of patient recovery (physical comfort, pain, physical independence, psychological support and emotional state) using a 5-point Likert Scale. Data was collected and analysed using SPSS version 17 statistical software. Normally distributed interval data were recorded as mean $\pm$ SD or as number unless otherwise indicated. Students t test or Wilcoxon Ranksum test was used to assess mean VAS score. Chi square test or Fischers exact test was used for qualitative variables. A p value < 0.05 was considered significant.

Results

A total of 80 patients were included in the study. There were no dropouts.

The sedation score recorded on arrival in the PACU was similar in the two groups (Table 1).

Table 1: Postoperative Sedation Score

Sedation score	Group L	Group D	p value
1	8 (20%)	8 (20%)	
2	16 (40%)	16 (40%)	0.50
3	16 (40%)	16 (40%)	
Mean ±SD	2.25 ± 0.85	2.25 ± 0.85	1.00

The sedation score was similar in both groups (Score 1-awake, 2-sleepy but arousable and 3-sleepy difficult to awake).

Similarly the VAS scores at each measured time were similar in both groups in the first 24 hours postoperatively as was the mean score over 24 hrs (Table 2). In both groups, 6 out of 40 patients (15%) required injection diclofenac once for pain relief. There was no requirement of rescue

analgesia with tramadol or further injections with diclofenac. In a similar way, 4 patients in Group L and 4 in Group D had nausea and vomiting post-operatively and required a single dose of antiemetic (Table 2).

The mean time taken to achieve a PADSS score $\geq$ 9 in Group L was 39.75 ± 11.17 minutes whereas in Group D it was 33.17 ± 6.27 minutes (p= 0.02). (Table 2).

Table 2: Postoperative observations

	Group L	Group D	p value
Requirement of additional postoperative analgesia (number of patients)	6 (15%)	6 (15%)	1.00
Postoperative nausea & vomiting (number of patients)	4 (10%)	4 (10%)	1.00
Requirement of Anti-emetics (number of patients)	4 (10%)	4 (10%)	1.00
VAS score over 24 hr (mean ±SD)	0.52 ± 0.74	0.41 ± 0.73	0.15
Time taken in minutes to achieve PADSS score ≥ 9 (mean ±SD)	39.75 ± 11.17	33.17 ± 6.27	0.02

A PADSS score $\geq$ 9 was achieved significantly faster in Group D as compared to Group L (VAS: Visual analogue scale, PADSS: Post anaesthesia discharge scoring system).
Group D patients also had a better quality of recovery as assessed by the QoR score. The combined score and the scores under each domain i.e. emotional state, physical comfort, psychological support, physical independence and pain were all better in Group D as compared to Group L (Table 3).

Table 3: The Quality of Recovery Score in Group L and Group D.

QoR domain	Group L (Mean ± SD)	Group D (Mean ±SD)	p value
Emotional State	44.30 ± 0.66	44.75 ± 0.44	0.01
Physical Comfort	58.55 ± 1.43	59.40 ± 0.50	0.01
Psychological Support	34.70 ± 0.47	35.00 ± 0.00	0.007
Physical Independence	24.65 ± 0.59	24.95 ± 0.22	0.03
Pain	34.55 ± 0.60	34.90 ± 0.31	0.02
Combined QoR score	196.65 ± 2.16	199 ± 0.92	0.0001

The Quality of Recovery Score – combined score and all domains - was significantly higher in Group D as compared to Group L.

Discussion
Perioperative infusions of dexmedetomidine and lidocaine were found to provide a similar analgesic sparing effect and postoperative pain relief in patients after laparoscopic cholecystectomy. However, the use of dexmedetomidine resulted in an earlier and better postoperative recovery. Multimodal analgesia has been recommended to reduce postoperative pain. [8] However, in spite of multi-pharmacological intervention, postoperative analgesia has not been consistently satisfactory. More recently, adjuvants such as lidocaine and dexmedetomidine have been suggested to reduce opioid consumption and facilitate recovery [9].
Various investigators have reported lesser postoperative pain in patients receiving lidocaine infusion during laparoscopic cholecystectomy [3, 10, 11]. Ram and colleagues [12] reported significantly lower VAS scores with intravenous rather than intraperitoneal lidocaine. The VAS scores decreased to a nadir at about 8 hours postoperatively. In the present study the mean VAS score in Group L over 24 hours was 0.52 ± 0.74 and showed a nadir at 8 hours (mean pain score 0.15 ± 0.36) after which the pain scores showed a steady rise. The half-life of lidocaine has been reported to be about 100 minutes following bolus injection or infusions lasting less than 12 hours [2]. This may explain the lower pain scores in the early postoperative period after lidocaine [10, 13].

Salman and colleagues [14] studied dexmedetomidine and remifentanil infusions in gynaecologic laparoscopic surgery. Dexmedetomidine caused a relatively slow recovery with reduced PONV and analgesic requirements and provided haemodynamic stability similar to remifentanil. In the present study, the mean 24 hr VAS score was 0.41± 0.73 in Group D. Unlike in the lidocaine group, the pain scores in Group D were lowest at about 24 hours. The context-sensitive half-life of dexmedetomidine infusion is influenced by age, sex, body weight, lean body mass, body surface area and albumin concentration. The present study included only female patients with lower body weight, body surface area and albumin levels as compared to male counterparts resulting in attainment of therapeutic steady state levels for prolonged periods which may explain the extended analgesic effect. The mean VAS scores over 24 hrs was however similar in Group L and Group D (p=0.15). In 2014, Kwangrae Cho [8] found no significant difference in VAS score or consumption of postoperative analgesics after laparoscopic cholecystectomy in patients receiving perioperative infusions of lidocaine and dexmedetomidine. They also reported no significant difference between dexmedetomidine and lidocaine with regard to the analgesic sparing effect. Other investigators have also found a reduced requirement for postoperative analgesics in patients receiving intraoperative lidocaine infusion [1, 2, 3, 4, 15, 16]. Low dose dexmedetomidine infusion also effectively attenuates haemodynamic stress responses during laparoscopic surgery with reduction in postoperative analgesic requirements [17]. Our study demonstrates an equally effective post-operative pain relief and analgesic sparing effect in both the study groups.
While evidence of lidocaine toxicity commences at plasma concentrations > 5 μg ml^{-1}, convulsive seizures occur at concentrations of 10-15 μg ml^{-1}, while cardiovascular depression requires plasma levels > 25 μg ml^{-1}. After an IV bolus of 1.5 mg kg^{-1} lidocaine followed by infusion of 1.5 mg kg^{-1} hr^{-1} that ended 60 min after skin closure, mean plasma lidocaine and monoethylglycinexylidide levels were found to be 2.1 ± 0.4 μg ml^{-1} and 0.3 ± 0.2 μg ml^{-1} respectively and none approached toxic levels [18]. Several investigators [2, 19] have reported plasma lidocaine concentrations well below toxic levels in patients receiving lidocaine infusions. The doses used in the present study were similar to those used in these previous studies and similar to those used to treat cardiac arrhythmias.
There are concerns of sedation after the use of dexmedetomidine and an infusion causes a relatively slow recovery [20, 21]. Hall [21] reported that dexmedetomidine infusions results in reversible sedation, mild analgesia, and memory impairment without cardiorespiratory compromise.

Cho [8] compared sedation scores upon arrival in PACU after intravenous lidocaine 1.5 mg kg^{-1} followed by infusion of 2 mg kg^{-1} hr^{-1} and intravenous dexmedetomidine 1 µg kg^{-1}, followed by infusion of 0.4 µg kg^{-1} hr^{-1}. They found that time taken to tracheal extubation was similar in both groups but while 23/28 patients receiving dexmedetomidine were not completely alert on PACU arrival, they all became completely alert twenty minutes later. The subsequent length of PACU stay was significantly shorter in the dexmedetomidine group. Thus patients receiving dexmedetomidine may show significant sedation for a short period, but this delayed recovery is not a cause of concern due to the short elimination time and lack of associated respiratory depression. On the other hand, lidocaine infusion is not associated with significant sedation. In our study, 40% of patients in both the groups had scores of 2 and 40% had scores of 3 with similar mean sedation scores i.e. 2.25 ± 0.85. (p= 1.00) on arrival in PACU.

Lidocaine infusions are also beneficial in attenuating intraoperative hemodynamic responses [22]. Dexmedetomidine shows biphasic cardiovascular changes and dose-dependent hemodynamic effects and is effective in attenuating stress responses during surgery and maintaining haemodynamic stability [20, 23]. In the present study there were no episodes of hypotension or bradycardia in the dexmedetomidine group and lidocaine seemed to be as effective as dexmedetomidine in attenuating haemodynamic stress responses during laparoscopic surgery.

We assessed the recovery profile using the modified PADSS and QoR 40 scores. While the mean time taken to achieve a PADSS score ≥ 9 in Group L was 39.75 ± 11.17 minutes, it was 33.17 ± 6.27 minutes in Group D. This difference was statistically significant (p= 0.02). Although a difference in mean time of about 6 minutes may not seem clinically significant it may become significant in centres handling large patient volumes. The use of lidocaine infusions have been found to shorten hospital stay [4, 19, 24]. Two recent meta-analysis, suggest that intravenous lidocaine during and after abdominal surgery reduced postoperative pain and opioid consumption, facilitated GI function, and shortened length of hospital stay [16, 25]. The QoR Score was first used by Myles P and colleagues [6] and has been validated as a tool for assessing overall recovery. It examines emotional state, physical comfort, psychological support, physical independence and pain. [Annexure1] Systemic lidocaine has been found to improve postoperative quality of recovery in patients undergoing outpatient laparoscopy [4, 26] using the QoR 40 questionnaire as the primary outcome variable. An inverse association has been reported between postoperative opioid consumption and the quality of recovery. As improved postoperative recovery may be due to a lowering of opioid consumption, we hypothesised that dexmedetomidine which has an opioid sparing effect and provides hemodynamic stability during laparoscopic surgeries may provide a superior quality of overall recovery. Our results showed that all domains of the QoR score were significantly better in Group D as compared to Group L (Table 3).

Although perioperative infusions of lidocaine and dexmedetomidine had similar haemodynamic effects and provided similar pain relief and reduction in analgesic consumption, the postoperative recovery profile was significantly better with dexmedetomidine. We suggest the use of perioperative dexmedetomidine as a superior adjuvant in laparoscopic cholecystectomy for providing postoperative pain relief and early recovery. Further studies are required in patients with underlying cardiovascular disease and dose response studies are required to elicit the optimum dose for this purpose.

Annexure 1: QoR 40 Questionnaire

S. No.	Question	None of the time	Some of the time	Usually	Most of the time	All of the time
1.	Able to breathe easy	1	2	3	4	5
2.	Feeling comfortable	1	2	3	4	5
3.	Able to return to work, or usual daily activities	1	2	3	4	5
4.	Able to write	1	2	3	4	5
5.	Have a good sleep	1	2	3	4	5
6.	Have normal speech	1	2	3	4	5
7.	Able to wash, brush teeth or shave	1	2	3	4	5
8.	Able to look after own appearance	1	2	3	4	5
9.	Having a general feeling of well-being	1	2	3	4	5
10.	Being able to enjoy food	1	2	3	4	5
11.	Feeling rested	1	2	3	4	5
12.	Feeling in control	1	2	3	4	5
13.	Able to communicate with hospital staff	1	2	3	4	5
14.	Able to communicate with family or friends	1	2	3	4	5
15.	Getting support from hospital doctors	1	2	3	4	5
16.	Getting support from hospital nurses	1	2	3	4	5
17.	Having support from family or friends	1	2	3	4	5
18.	Able to understand instructions or advice	1	2	3	4	5
19.	Nausea	5	4	3	2	1
20.	Vomiting	5	4	3	2	1
21.	Dry retching	5	4	3	2	1
22.	Moderate pain	5	4	3	2	1
23.	Severe pain	5	4	3	2	1
24.	Feeling restless	5	4	3	2	1
25.	Shaking or twitching	5	4	3	2	1
26.	Shivering	5	4	3	2	1

27.	Feeling too cold	5	4	3	2	1
28.	Bad dreams	5	4	3	2	1
29.	Headache	5	4	3	2	1
30.	Muscle pains	5	4	3	2	1
31.	Backache	5	4	3	2	1
32.	Sore throat	5	4	3	2	1
33.	Sore mouth	5	4	3	2	1
34.	Feeling dizzy	5	4	3	2	1
35.	Feeling confused	5	4	3	2	1
36.	Feeling anxious	5	4	3	2	1
37.	Feeling angry	5	4	3	2	1
38.	Feeling depressed	5	4	3	2	1
39.	Feeling alone	5	4	3	2	1
40.	Difficulty falling asleep	5	4	3	2	1
	Total Score:					

Conclusion

Perioperative infusions of lidocaine and dexmedetomidine had similar effect on postoperative pain relief and reduction in analgesic consumptions. However, the postoperative recovery profile was better with dexmedetomidine infusion. We suggest the use of perioperative dexmedetomidine in laparoscopic cholecystectomy for postoperative pain relief as it reduces opioid consumption and provides early recovery.

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