Effect of intraperitoneal instillation of dexmedetomidine or fentanyl as adjuvants to bupivacaine on fast tracking discharge criteria in patients undergoing ambulatory laparoscopic cholecystectomy: a randomised double-blind control trial

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Abstract

Background: Postoperative analgesia in laparoscopic cholecystectomy significantly affects the ambulation and discharge of the patient. This study compares fentanyl and dexmedetomidine as adjuvants to bupivacaine in intraperitoneal instillation after LC, in terms of their impact on ambulation, analgesic efficacy and recovery profile. Ninety patients were randomised into three groups with thirty patients in each group; group BF was administered 20 ml of 2 μg/kg fentanyl + 0.25% bupivacaine, group BD received 20 ml of 1 μg/kg dexmedetomidine + 0.25% bupivacaine and group B received 20 ml of 0.25% bupivacaine only. After 8 h, Post-Anaesthesia Discharge Scoring System (PADS) scored for determining home readiness. Analgesic profile was assessed using Verbal Rating Scale and rescue analgesia requirement seen. Sedation was scored using Ramsay sedation scoring.

Results: Group B had significantly higher VRS and rescue analgesia requirements whilst groups BF and BD had a similar analgesic profile. Ramsay sedation scores were significantly higher in group BD when compared to groups BF and B. However, the PADS score remained comparable in all three groups (P = 0.113). The trial was retrospectively registered with the clinical trial registry of India CTRI/2019/07/020466.

Conclusion: Intraperitoneal instillation of bupivacaine in combination with dexmedetomidine or fentanyl significantly reduces postoperative pain scores in comparison to bupivacaine alone, in patients undergoing ambulatory laparoscopic cholecystectomy. However, fentanyl may be preferred over dexmedetomidine, because it causes less sedation and achieves a better PADS score.

Keywords: Dexmedetomidine, Pain, Postoperative, Fentanyl, Bupivacaine
Background
Laparoscopic cholecystectomy (LC) is the most accepted surgical technique for cholelithiasis as compared to open cholecystectomy. Laparoscopic procedures have many advantages over open procedures such as lesser haemorrhage, better cosmetic results, lesser postoperative pain and shorter recovery time leading to a shorter hospital stay and less expenditure (Bisgaard et al., 2001).

But even LC is associated with postoperative pain affecting early ambulation of the patient. Pain in laparoscopic surgery results from stretching of the abdominal cavity, peritoneal inflammation, diaphragmatic irritation and residual carbon dioxide (CO₂) in the peritoneal cavity. Peritoneal irritation by carbonic acid (formed by reaction between carbon dioxide CO₂ and water) and the creation of space between the liver and diaphragm by residual pneumoperitoneum has been implicated for visceral and shoulder tip pain. Humidity and volume of the insufflated gas, wound size and trauma to the parietal peritoneum may also be responsible for this pain (Alexander & Hull, 1987; Mouton et al., 1999).

A multimodal approach is required to alleviate all three types of pain which includes parenteral NSAIDs, opioids, and postoperative intraperitoneal local anaesthetic instillation, post-site infiltration of local anaesthetic, intraperitoneal saline, removal of insufflation gas, gas drains, low-pressure abdominal insufflations, acetazolamide administration and use of N₂O in place of CO₂, etc (Woolf, 1983).

Intraperitoneal instillation of local anaesthetic agents has become an important method to control postoperative nausea and vomiting (PONV) and reduce hospital stay following LC. This approach is particularly useful as there is an increasing demand for ambulatory setting for LC. Intraperitoneal instillation of local anaesthetic agents alone (Ahmed, Abd Elmawgoud & Doaa, 2008) or in combination with opioids and α₂ agonists such as clonidine and dexmedetomidine has been found to reduce postoperative pain following LC (Marshall & Chung, 1999).

Since there are a few studies which have compared the nociceptive effects of intraperitoneal fentanyl to intraperitoneal dexmedetomidine, the present study was undertaken to compare the effects of intraperitoneal bupivacaine with dexmedetomidine or fentanyl as adjuvants, in patients undergoing ambulatory laparoscopic cholecystectomy (ALC). The aim was to assess the recovery profile of patients and to compare the analgesic efficacy of intraperitoneal bupivacaine with dexmedetomidine or fentanyl as adjuvants, in patients undergoing ambulatory laparoscopic cholecystectomy.

The secondary outcome was to assess postoperative analgesia, the requirement of rescue analgesia, haemodynamic stability and other side effects.

Methods
After obtaining approval from Institution Ethics Committee, ninety patients, in the age group of 18—60 years belonging to ASA physical status I and II, undergoing ambulatory laparoscopic cholecystectomy for symptomatic cholecystitis and cholelithiasis were included, and written informed consent was taken. The study was conducted over a period of 1 year. The patients with BMI less than 18 or > 30 kg/m², with psychiatric illness and with coagulation disorders; those allergic to local anaesthetics, dexmedetomidine or fentanyl; and patients with heart block or heart rate less than 50 bpm were excluded. Intraoperatively, patients who were converted into open cholecystectomy and had a bleeding liver bed, in whom the drains were kept, were also excluded.

Randomisation was done by a computer-generated randomised number table. Random numbers were enclosed in a sealed opaque envelope and opened by one of the investigators to know the study drug/combination to be administered, only after shifting of the patient inside the operation theatre. The operating surgeon and observer anaesthetist who collected the postoperative data were blinded to the test drug/combination administered through the laparoscopic port intraperitoneally.

Patients were educated about the 10-point Verbal Rating Score (VRS) 1 day prior to surgery where 0 is no pain and 10 is the worst imaginable pain. All patients were pre-medicated with oral alprazolam 0.25 mg the night prior and in the morning of the surgery.

According to the random number, the patients were allocated to one of the three groups:

Group B (bupivacaine group) received 20 ml of 0.25% bupivacaine (10 ml of 0.5% bupivacaine diluted to a total of 20 ml with 0.9% NS) intraperitoneally over the liver bed through the instillation port of the laparoscope. Group BD (dexmedetomidine group) received 20 ml of 0.25% bupivacaine + 1 μg/kg of dexmedetomidine (10 ml of 0.5% bupivacaine + 1μg/kg of dexmedetomidine, diluted to a total of 20 ml with 0.9% NS) intraperitoneally over the liver bed through the instillation port of the laparoscope.

Group BF (fentanyl group) received 20 ml of 0.25% bupivacaine + 2μg/kg of fentanyl (10 ml of 0.5% bupivacaine + 2μg/kg of fentanyl, diluted to a total of 20 ml with 0.9% NS) intraperitoneally over the liver bed through the instillation port of the laparoscope.

On arrival to the operation theatre, a peripheral intravenous line was established with an 18G cannula on the non-dominant hand. The patients were monitored with standard five-lead ECG (electrocardiography), heart rate, non-invasive blood pressure (NIBP) and pulse oximeter. Patients were induced with 2 μg/kg fentanyl and propofol till the verbal response was lost. The muscle relaxation was achieved with atracurium 0.5 mg/kg, the
anaesthesia was maintained with sevoflurane and the trachea was intubated with an appropriate size endotracheal tube after 3 min. The anaesthesia was maintained with admixture of oxygen + nitrous oxide and sevoflurane to achieve the MAC of 1.3 and maintained with top up of injection atracurium (0.1 mg/kg) as a muscle relaxant.

Pre-incisional infiltration was done by the surgeon using 20 ml of 0.25% bupivacaine (5 ml for each port). Injection ondansetron 4mg and injection dexamethasone 0.1 mg/kg were given intravenously. The patients were given injection diclofenac 75 mg intravenous in 100ml NS and infusion paracetamol 1 g. The intraperitoneal instillation of the test drug was done by the same operating surgeon after the gall bladder was taken out and the peritoneal wash had been done. At the end of the surgery, residual neuromuscular blockade was reversed with injection neostigmine 0.05 mg/kg with injection glycopyrrolate 0.01 mg/kg and tracheal extubation was performed as per standard anaesthesia protocol.

Data were collected after the patient was shifted to PACU. Heart rate, systolic and diastolic blood pressure, MAP and SpO₂ were recorded at 0, 1, 2, 4, 6 and 8 h of intervals after surgery. The time 0 started when the patient was shifted to PACU. If heart rate was less than 50 beats per minute, injection atropine was given. Injection mephentermine was given in 3 mg bolus if the mean arterial pressure was less than 20% of the baseline.

The patients were scored using Post-Anaesthesia Discharge Scoring System (PADS) for determining home readiness (Kahokehr et al., 2011) at 8 h from surgery. The total possible score was 10; a patient scoring ≥ 9 was considered fit for discharge. It included vital signs, activity level, nausea and vomiting, pain and surgical bleeding. When the VRS score was more than 3, injection diclofenac 75 mg intravenous was administered as an infusion in 100 ml normal saline.

Sedation was graded using the Modified Ramsay Sedation Scale. Postoperative nausea and vomiting (PONV) was rated as 0—no nausea or vomiting, 1—nausea but no episode of vomiting, and 2 if an episode of vomiting is present.

Data were presented as frequency, mean and standard deviation whenever applicable. Categorical variables between the 2 groups were compared using the chi-square test of Fischer exact test. One-way ANOVA followed by post hoc analysis (Bonferroni) was used to compare quantitative variables between 3 groups. P value < 0.05 was considered significant. Statistical analysis was performed using SPSS 21.

Results

A total of 90 patients were enrolled in the study and divided into three groups—B, BD and BF (Fig. 1).

The demographic data was comparable amongst all the groups (Table 1).

The PADS score of 9 and more was achieved by all the patients in all the three groups. All the patients met with the discharge criteria at the end of 8 h indicating that the patients in all the three groups were

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**Fig. 1** Consort flow diagram
comfortable with regard to analgesia, PONV and sedation. All the patients were ambulatory at the end of 8 h (Table 2).

The heart rate, mean arterial pressure and saturation of peripheral oxygen (SpO₂) were within the normal range and were comparable in all the three groups in the postoperative period for the next 8 h.

The pain score verbal rating score (VRS) was analysed at 1h, 2 h, 4h, 6 h and 8 h and found to be more in the B group as compared to the BD and BF groups. The difference was statistically significant for bupivacaine as compared to the fentanyl group as well as the dexmedetomidine group. The scores were comparable between the fentanyl and dexmedetomidine groups (Table 3) (Fig. 2).

The sedation score was assessed with the Ramsay sedation score and was more with the BD group as compared to the BF and B groups at all time points at 0h, 1h, 2 h, 4h, 6 h and 8 h and was statistically significant. The sedation was more with fentanyl as compared to bupivacaine plain at 0 h and 1 h and was statistically significant. The sedation score was the same after 1 h with fentanyl and bupivacaine. However, the sedation score was not more than three at any point so all patients were arousable and did not need any intervention (Fig. 3).

The rescue analgesia was administered in the form of Inj. diclofenac 75 mg intravenous, and 13, 8 and 9 patients in bupivacaine, dexmedetomidine and fentanyl groups required analgesia and the rescue analgesia requirement was not statistically significant amongst the three groups (Fig. 4). The incidence of postoperative nausea and vomiting was comparable in all the three groups at the end of 8 h.

Discussion
The postoperative period after LC follows a very short course, allowing patients to rapidly reinitiate oral intake and begin walking. Likewise, the intraoperative time of this technique has been progressively reduced. These factors provide the possibility of performing LC as ambulatory surgery (ALC). Pain is often the main reason for staying overnight in the hospital on the day of surgery and is the dominant complaint and the primary reason for prolonged convalescence after laparoscopic surgery. The rationale for intraperitoneal administration of drugs is that the small incisions at the abdominal wall cause visceral component of the pain and shoulder pain. With this in mind, many authors have tried to diminish pain via the peritoneal route. IPLA is likely to block free afferent nerve endings in the peritoneum. Systemic absorption of LA from the peritoneal cavity may also play a part in reduced nociception although this would be expected to occur after any LA technique (Gupta et al., 2010).

The present study was aimed to compare the analgesic efficacy of intraperitoneal bupivacaine with dexmedetomidine or fentanyl and to compare their effect on early ambulation in patients undergoing laparoscopic cholecystectomy. In the present study, postoperative PADS and VRS score was observed up to 8 h to see the readiness for discharge. We observed that a discharge criterion (PADS) was much favourable in the patients receiving fentanyl in adjunct to bupivacaine as compared to the other two groups. This observation could be attributed to the fact that patients who received dexmedetomidine with bupivacaine had a higher sedation score, hence lower discharge credibility. Other criteria used in PADS were VRS, haemodynamic stability in the form of HR, blood pressure, PONV, activity level and surgical bleeding.

There was a statistically significant difference in the VRS score between the groups, i.e. it was lower when either dexmedetomidine or fentanyl was added to bupivacaine in comparison to bupivacaine alone at all time intervals up to 8 h. However, there was no statistically significant difference in the VRS score between bupivacaine-dexmedetomidine and bupivacaine-fentanyl groups. Our study observed that the number of patients

| Table 1 Demographic variables | Group B (n = 30) | Group BD (n = 30) | Group BF (n = 30) | P value |
|--------------------------------|-----------------|------------------|------------------|---------|
| Age (years)                    | 40.13 ± 11.09   | 46.00 ± 9.49     | 41.93 ± 11.04    | 0.094   |
| Sex (M:F)                      | 4:26            | 3:27             | 5:25             | 0.749   |
| BMI (kg/m²)                    | 22.72 ± 2.19    | 21.95 ± 2.12     | 22.34 ± 2.31     | 0.404   |

Data shown as mean ± SD or frequency (percentage); ¹one-way ANOVA; ²chi-square test

| Table 2 Comparison of PADS in group B, group BD, and group BF | Group B (n = 30) | Group BD (n = 30) | Group BF (n = 30) | P value |
|----------------------------------------------------------------|-----------------|------------------|------------------|---------|
| Total score                                                   | 9               | 20               | 12               | 0.113   |
|                                                              | 10              | 10               | 18               | 28      |
who required rescue analgesia was higher in group B as compared to the dexmedetomidine and fentanyl groups but it was not statistically significant. Gupta et al. conducted a study to compare the effectiveness of intraperitoneal bupivacaine with or without fentanyl for postoperative analgesia after laparoscopic surgery and found that 20 ml of 0.5% bupivacaine + 100 μg fentanyl significantly reduced the immediate postoperative pain (VAS 40.1 ± 9.8 vs. 65.2 ± 9.5; VRS 2.2 ± 0.4 vs. 3.8 ± 0.4). It also reduced the intensity of pain even after 24 h (VRS 40.3 ± 7.4 vs. 50.1 ± 7.8; VRS 3.50 ± 1.2 vs. 4.23 ± 0.78). Total analgesic consumption was also less in the fentanyl + bupivacaine group (Elnabtity & Ibrahim, 2018).

Similarly, Elnabtity and Ibrahim (Oza et al., 2016) compared the postoperative pain when intraperitoneal bupivacaine (0.25%) is administered alone versus the addition of dexmedetomidine (1 μg/kg) to it in 52 children undergoing a laparoscopic appendectomy in a prospective randomised trial. Postoperative visual analogue scale scores were lower in the dexmedetomidine group at 2, 4 and 6 h (mean = 3, 3, 3, respectively) compared with the plain bupivacaine group (mean = 4, 5, 4, respectively) (P < 0.05) but had more sedation scores at 0, 2 and 4 h (P < 0.05), longer time to first rescue analgesia (P = 0.03), lesser rescue analgesic consumption (P = 0.02), shorter length of hospital stay (P = 0.02) and higher parents’ satisfaction (P = 0.01). They concluded that adding dexmedetomidine to intraperitoneal bupivacaine provides adequate postoperative analgesia in children undergoing laparoscopic appendectomy. The study results were in accordance with our study.

It was observed that the addition of dexmedetomidine or fentanyl to bupivacaine was not associated with postoperative nausea and vomiting in the present study. Oza et al. (Bakhamees et al., 2007) in a similar study compared intraperitoneal instillation of 50 ml of bupivacaine 0.25% (125 mg) to 50 ml of bupivacaine 0.25% (125 mg) + 1 μg/kg of dexmedetomidine. They observed that the incidence of postoperative nausea and vomiting was comparable in both groups. Similar results have also been shown by Bakhamees et al. (12). Similarly, in our study, the incidence of the PONV was insignificant.

Intraperitoneal instillation of local anaesthetic is an easy, cheap and non-invasive method that provides good analgesia in the immediate postoperative period after laparoscopic surgery. The combination of intraperitoneal bupivacaine and dexmedetomidine or fentanyl as an

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**Table 3** Comparison of pain scores at different time intervals

| VRS  | Group B (n = 30) | Group BD (n = 30) | Group BF (n = 30) | P value | Post hoc |
|------|-----------------|-----------------|-----------------|---------|---------|
| 0 min| 2.23 ± 0.82     | 1.80 ± 0.41     | 1.77 ± 0.50     | 0.005**| B vs. BD = 0.020*; B vs. BF = 0.010**; BD vs. BF = 1.000 |
| 1 h  | 2.33 ± 1.06     | 1.57 ± 1.41     | 1.37 ± 0.77     | 0.003**| B vs. BD = 0.027*; B vs. BF = 0.003**; BD vs. BF = 1.000 |
| 2 h  | 2.30 ± 1.12     | 1.67 ± 1.24     | 1.53 ± 1.11     | 0.027* | B vs. BD = 0.110; B vs. BF = 0.036*; BD vs. BF = 1.000 |
| 4 h  | 2.97 ± 0.81     | 1.77 ± 1.48     | 1.67 ± 0.84     | <0.0001***| B vs. BD < 0.0001***; B vs. BF < 0.0001***; BD vs. BF = 1.000 |
| 6 h  | 2.40 ± 1.13     | 1.57 ± 0.77     | 1.37 ± 0.93     | <0.0001***| B vs. BD = 0.003**; B vs. BF < 0.0001***; BD vs. BF = 1.000 |
| 8 h  | 2.30 ± 0.70     | 1.60 ± 0.93     | 1.33 ± 0.92     | <0.0001***| B vs. BD = 0.007**; B vs. BF < 0.0001***; BD vs. BF = 0.697 |

Data shown as mean ± SD; one-way ANOVA followed by Bonferroni post hoc; *significant; **highly significant; ***very highly significant

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**Fig. 2** Comparison of pain score amongst the three groups
adjuvant is superior to plain bupivacaine for reducing postoperative pain in patients who underwent ALC, without any significant adverse events. Both dexmedetomidine and fentanyl when used with bupivacaine reduce not only the intensity of pain but also the rescue analgesia consumption, thereby facilitating early ambulation of the patients. Although dexmedetomidine and fentanyl provide comparable analgesia when combined with bupivacaine, the comparatively higher sedation observed with dexmedetomidine may hamper early ambulation. This makes fentanyl a more attractive option when an early discharge is planned.

**Conclusion**

Intraperitoneal instillation of bupivacaine in combination with dexmedetomidine or fentanyl significantly reduces postoperative pain scores in comparison to bupivacaine alone, in patients undergoing ambulatory laparoscopic cholecystectomy. Since early ambulation is desired, significantly higher sedation scores seen with dexmedetomidine can lead to a delayed resumption of activity and delayed discharge. Hence, fentanyl may be preferred over dexmedetomidine, because it causes less sedation and achieves a better PADS score.
Abbreviations
LC: Laparoscopic cholecystectomy; IPLA: Intraperitoneal instillation of local anaesthetic; PADS: Post-anaesthesia discharge scoring system; CO₂: Carbon dioxide; NSAIDS: Non-steroidal anti-inflammatory drugs; N₂O: Nitrous oxide; PONV: Postoperative nausea and vomiting; ALC: Ambulatory laparoscopic cholecystectomy; ASA: American society of anaesthesiologists; VRS: Verbal rating score; ECG: Electrocardiography; NIBP: Non-invasive blood pressure; MAC: Minimum alveolar concentration; PACU: Post-anaesthesia care unit; MAP: Mean arterial pressure; SpO₂: Saturation

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Authors’ contributions
BG conceptualised and designed the study. VV analysed and interpreted the patient data. UK analysed the data and contributed in writing the manuscript. RD drafted the work and revised it. AC drafted the manuscript and helped in the acquisition of the data. All authors read and approved the final manuscript.

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Declarations
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Written consent was taken from the study participants.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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