

Comparison of effect of intraperitoneal instillation of additional dexmedetomidine or clonidine along with bupivacaine for post-operative analgesia following laparoscopic cholecystectomy

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ABSTRACT

Background and Aims: Despite advances in minimally invasive surgery, postoperative pain remains a concern after laparoscopic cholecystectomy. This study aims to compare the effect of intraperitoneal instillation of bupivacaine with alpha-2 agonists (dexmedetomidine and clonidine) for postoperative analgesia. **Methods:** One hundred and eight patients scheduled for elective laparoscopic cholecystectomy were randomised to receive either 20 mL of 0.5% bupivacaine (Group B), 20 mL of 0.5% bupivacaine with dexmedetomidine 1 µg/kg (Group BD) or 20 mL of 0.5% bupivacaine with clonidine 1 µg/kg (Group BC). Study drug made to equal volume (40 mL) was instilled before the removal of trocar at the end of surgery. Standard general endotracheal anaesthesia with intra-abdominal pressure of 12–14 mm Hg during laparoscopy was followed uniformly. The primary objective of our study was the magnitude of pain. One way analysis of variance (ANOVA) for continuous variables and Chi-square test for categorical variables was used. **Results:** The Numerical Rating Scale (NRS) scores for pain intensity did not show any statistical significance at any of the pre-defined time points. Time to first request for analgesia was shortest in group BC (64.0 ± 60.6 min) when compared to the other groups (B, 78.8 ± 83.4 min; BD, 112.2 ± 93.4 min; $P < 0.05$). Total amount of rescue fentanyl given in groups BD (16.8 ± 29.0 µg) and BC (15 ± 26.4 µg) was significantly less than B (35.7 ± 40.0 µg); $P < 0.05$. **Conclusion:** The addition of alpha-2 agonists to bupivacaine reduces the post-operative opioid consumption, and dexmedetomidine appears to be superior to clonidine in prolonging time to first analgesic request.

Key words: Analgesia, cholecystectomy, laparoscopic, postoperative period

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INTRODUCTION

Inflammation and dissection around the gall bladder bed and capnoperitoneum are the main reasons for visceral pain.^[1] Shoulder pain is mainly due to phrenic nerve neuropraxia and increased intra-abdominal pressure leading to stretching of subdiaphragmatic fibres.^[2,3] Among various multimodal methods for post-operative analgesia, intraperitoneal (IP) instillation of local anaesthetics with adjuvants remains a popular method among anaesthesiologists. Both clonidine and dexmedetomidine have been tried separately with a placebo control to provide an extended period of post-operative analgesia.^[4,5] A recent editorial outlines

the off-label uses of dexmedetomidine in various clinical scenarios through several routes.^[6] However, we have not come across any study directly comparing

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the effects of clonidine with dexmedetomidine along with bupivacaine for extended post-operative analgesia in laparoscopic cholecystectomy. The objectives have been defined as primary and secondary outcomes. The primary objective of our study was the magnitude of pain assessed by Numerical Rating Scale (NRS) score and secondary objectives were time to first request for analgesia, an analgesic requirement in the first 24 h postoperatively, incidence of shoulder pain in the study groups and adverse effects during the study period. We hypothesised that the addition of dexmedetomidine or clonidine to bupivacaine intraperitoneally significantly reduces the amount of opioid consumption postoperatively, and IP dexmedetomidine along with bupivacaine provides a longer period of post-operative analgesia when compared to clonidine.

METHODS

This prospective, randomised, double-blind controlled study was conducted in a tertiary care teaching hospital after taking approval from the Institutional Ethics committee and registration of the trial in Clinical Trials Registry-India (CTRI). Written informed consent was obtained from all the study participants. The study period was 1 year (01/04/2018 to 01/04/2019).

One hundred and eight patients belonging to the American Society of Anesthesiologists physical status (ASA-PS) I/II, aged between 18 and 60 years, of either gender posted for elective laparoscopic cholecystectomy under general anaesthesia were included. The patients allergic to study drugs, pregnant or lactating mothers, severe cardiac, pulmonary, and renal disease, insertion of a drain at the end of the procedure, unwilling to participate in the study, unable to give informed consent, unable to understand or interpret NRS for pain were excluded from the study. Patients needing conversion to open cholecystectomy were excluded from the final analysis.

The patients were randomly allocated to one of the three groups by a computer-generated random number table and group allocated by sealed opaque envelope technique. Blinding was ensured by having an independent anaesthesiologist not participating in the study to prepare the study drug in a ready to inject form for a total volume of 40 mL.

Each group comprising 36 participants received either 20 mL of 0.5% bupivacaine (Group B), 20 mL of 0.5% bupivacaine with dexmedetomidine 1 μ /kg (Group BD), or 20 mL of 0.5% bupivacaine with clonidine 1 μ /kg

(Group BC) before the removal of trocar at the end of surgery. All the study drugs were made into an equal volume of 40 mL each by adding 0.9% normal saline.

Preoperatively, all the patients were explained about the study protocol and how to use NRS to indicate their pain perception by identifying zero/0 as no pain and ten/10 as worst imaginable pain during pre-anaesthetic check-up and re-explained the day before surgery while prescribing premedication. An 18 G intravenous cannula under local anaesthesia was secured on the dorsum of the hand after patient arrival and standard monitoring like three lead electrocardiography, noninvasive blood pressure, saturation by pulse oximetry, and end-tidal carbon dioxide (CO₂) were connected, and baseline vital parameters noted. A standard general anaesthesia protocol comprising intravenous (IV) fentanyl 2 μ /kg, propofol 2 mg/kg, vecuronium bromide 0.1 mg/kg to facilitate orotracheal intubation was followed in all patients. Anaesthesia was maintained with oxygen and air with 0.5%–3% isoflurane. Minute ventilation was adjusted to maintain normocapnia (end-tidal CO₂ between 34 and 38 mm Hg). During laparoscopy, intraabdominal pressure was maintained between 12 and 14 mm Hg. Towards the end of skin closure and before removal of the trocar, 20 mL of the drug as per the random group allocation was instilled intraperitoneally at the gall bladder bed and 20 mL in the perihepatic space. At the end of the surgery, residual neuromuscular blockade was reversed with IV neostigmine and IV glycopyrrolate, and all the patients were shifted to the recovery room.

Post-operatively, the intensity of pain was recorded for all patients using NRS at 30 min, 1, 2, 4, 6, and 24 h after surgery. The total analgesic requirement in the first 24 h was noted. If NRS score >3, patients were prescribed paracetamol 15 mg/kg IV followed by additional doses if requested by the patient after an interval of 6 h, and pain between two doses of paracetamol was treated with fentanyl 1 μ g/kg IV. Time to first request for analgesia, the total dose of analgesics (paracetamol and fentanyl) given, the incidence of shoulder pain, adverse effects such as nausea, vomiting, pruritus, bradycardia (HR <50 bpm), hypotension (20% reduction in the baseline blood pressure), and rhythm disturbances on electrocardiography (ECG) were noted.

The primary outcome of our study was the magnitude of pain with reference to NRS score,

and secondary outcomes were time to first request for analgesia, an analgesic requirement in the first 24 h postoperatively, the incidence of shoulder pain in the study groups, adverse effects such as nausea, vomiting, pruritus, bradycardia, hypotension during the study period.

Shukla U *et al.*^[7] observed that the time to first analgesic request for their control group (bupivacaine alone) was 55 ± 18 min. We assumed that a 25% increase in the time to the first analgesic request would give a clinically meaningful effect size with a similar standard deviation. This yielded a sample size of 31 patients per group with an alpha error of 0.05 and 80% power of the study. Considering a drop out of five per group, we recruited a total of 108 patients for our study. The data obtained were evaluated for normality using the Shapiro–Wilk test. Quantitative data were expressed as mean \pm standard deviation or median (interquartile range 25%–75%)

and were analysed with one-way analysis of variance (ANOVA) (for normally distributed data) or Kruskal–Wallis test (for non-normally distributed data) as appropriate along with Bonferroni *post hoc* test to find out significance between the pairs. Descriptive variables were presented as frequency, percentage, or a number and were compared by Chi-square test or Fisher's Exact test as appropriate. *P* value < 0.05 was considered as significant. All statistical analyses were done using Statistical Package for the Social Sciences (SPSS) version 20 (International Business Machines (IBM) Inc. Chicago IL, USA, 2010).

RESULTS

In our study, out of 108 patients who entered the study pool, six patients were excluded/had fallen out of the study after randomisation due to drain insertion at the end of surgery. Our study comprised three groups (B, BD, BC), each of which consisted of 34, 33, and 35 subjects, respectively [Figure 1].

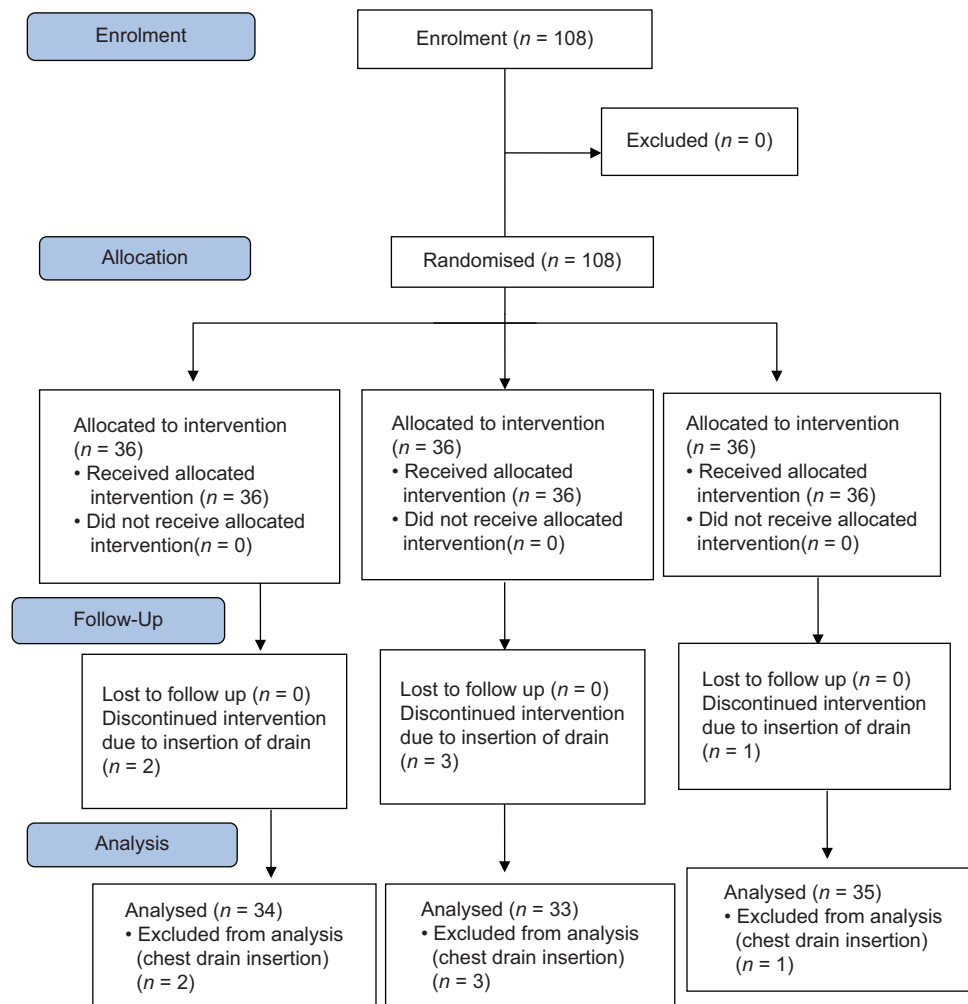


Figure 1: CONSORT Flow diagram

There were no significant differences among the three treatment groups in terms of patient demographics and operative data [Table 1].

The intensity of pain was recorded using NRS [Table 2] at specified time intervals i.e., 0.5, 1, 2, 4, 6, 24 h after surgery, and reversal from anaesthesia did not show any statistical significance.

The total amount of rescue fentanyl required was lower in group BD (16.8 ± 29.04) and group BC (15 ± 26.4) when compared to group B (35.73 ± 40.09); $P < 0.05$, and group BC required less amount of fentanyl when compared to group BD [Table 3]. The *post hoc* analysis revealed a significant difference between groups B and BC; $P < 0.05$ and trended towards significance between groups B and BD ($P = 0.05$).

The mean time to first request for analgesia in minutes was less in group BC (64.0 ± 60.69); [range 0–240 min] when compared to group BD (112.27 ± 93.4); [range 0–360 min] and group B (78.82 ± 83.4); [range 0–280 min]; $P < 0.05$ and the *post hoc* analysis between groups BD and BC showed significant difference ($P = 0.04$) [Table 3].

There was no difference statistically in the number of doses and total dose of paracetamol received among the groups.

There was a statistically significant difference between the groups in the total number of times a patient was given rescue analgesia. Fifteen among 34 patients from Group B received fentanyl once and nine patients among 33 and 35 patients from group BD and BC, respectively received fentanyl once; ($P = 0.008$). Significantly, a greater number of patients from group B required rescue fentanyl when compared to other study groups [Table 3]. Moreover, none of the patients from group BD and BC needed a second dose of rescue fentanyl in comparison with group B.

There was no incidence of adverse events such as nausea, vomiting, pruritus, bradycardia, and hypotension in any of the groups.

DISCUSSION

In spite of major advances in post-operative analgesic therapies nowadays, pain after laparoscopic cholecystectomy still remains a clinical challenge to the anaesthesiologist.

One of the major findings in our study is that the addition of alpha-2 agonists (clonidine and dexmedetomidine) to bupivacaine does not have any additional effect on the magnitude of postoperative pain compared to the control group at predefined time points in the first 24 h. This can be explained by insufficient afferent blockade i.e., intraperitoneal local anaesthetic instillation was done after skin incision, trocar insertion and creation of pneumoperitoneum, and the nociceptive input had already been established before intervention. This possible explanation was proved in a Turkish study where a comparison of intraabdominal and trocar site-local anaesthetic was done.^[8] Their study showed better analgesia in trocar site infiltration when compared to intraperitoneal instillation.

In a previous study conducted at our teaching hospital, pre-emptive vs post-emptive intraperitoneal LA instillation was compared.^[9] In contrast to our results with regard to pain intensity, at 30 min, the pain score was zero in all three groups which can be explained by additional intraoperative analgesic morphine 0.1 mg/kg given in that study.

The dose of bupivacaine used for intraperitoneal instillation varies not only in the amount administered (10–100 mL) but also in the different concentrations used (0.1%–0.5%) and timing of administration (before or after surgery). Overall,

Table 1: Demographic characteristics of patients and operative data

Variable	Group B (n=34)	Group BD (n=33)	Group BC (n=35)	P
Age (years)	45.3±10.4	44.7±11.4	41.0±12.1	0.242
Sex (Male/Female) (n)	18/16	13/22	15/18	0.419
Weight (kg)	66.6±12.8	64.2±12.9	61.0±12.1	0.185
BMI (kg/m ²)	27.0±4.0	26.4±2.8	26.4±4.2	0.746
ASA PS (I/II/III) (n)	25/9/0	23/10/0	29/6/0	0.428
Duration of surgery (min)	64.8±33.4	70.6±23.7	76.2±32.3	0.296
Duration of anaesthesia (min)	91.1±33.2	99.8±27.0	106.4±36.9	0.158

n=number of patients, BMI=Body mass index, ASAPS=American Society of Anesthesiologists Physical Status. Group B: Bupivacaine, Group BD: Bupivacaine and dexmedetomidine, Group BC: Bupivacaine and clonidine

there is no definitive consensus about the dose and concentration to be used for effective post-operative pain relief and most of our study subjects were average Indian adults weighing around 50 kg, and considering the toxic dose of bupivacaine i.e., ≤ 2 mg/kg, our trial participants were given 40 mL of 0.25% bupivacaine intraperitoneally which sums up to 100 mg.

Antinociceptive effects of intraperitoneal dexmedetomidine or tramadol combined with bupivacaine to intraperitoneal bupivacaine alone were compared in patients undergoing laparoscopic cholecystectomy in another study.^[7] Overall, VAS in 24 h in this study was significantly lower in the dexmedetomidine group when compared to the tramadol and placebo group. Few investigators did not find any significant difference in the magnitude of postoperative pain with the use of different types of local anaesthetics through the intraperitoneal route.^[10-12]

The subjective nature of quantification of pain and lack of definitive consensus about the dose and concentration of local anaesthetics to be used for effective post-operative pain relief while comparing different treatment options may be the reason for the contrary results noted between different studies.

In a meta-analysis done by A. Kahokehr and team, the concluded evidence was in favour of intraperitoneal local anaesthesia (IPLA) in laparoscopic gastric procedures for reduction of abdominal pain intensity, the incidence of shoulder pain, and post-operative opioid consumption.^[13] This is congruous to our study

where NRS scores in all the three groups at all the time points are less than 4, which in turn proclaims the efficacy of IPLA.

The total amount of rescue fentanyl used in dexmedetomidine and clonidine groups in the current study was significantly less when compared to the plain bupivacaine group ($P = 0.016$) with no significant difference between groups BD and BC. One such study similar to ours compared the effects of intraperitoneal instillation of levobupivacaine along with clonidine for pain relief after laparoscopic cholecystectomy, and it was opined that analgesic consumption was less in adjuvants group with alpha-2 agonists when compared to plain LA.^[14] This implies that alpha-2 agonists like clonidine have higher antinociceptive effects and provide better pain relief with a reduction in analgesics requirement postoperatively through their synergistic action when instilled intraperitoneally with LAs such as bupivacaine or levobupivacaine.

In line with our study, some investigators also observed a similar amount of opioid-sparing effect in the post-operative period when compared to the placebo group using dexmedetomidine through IV route.^[15-17]

The main limitation of our study was the non-inclusion of well-defined predictors of post-operative pain like pre-operative anxiety and pre-existing pain condition. The second limitation of our study was the failure to evaluate shoulder pain beyond 24 h.

The strong points in our study are that there is no head-on comparison of the two most commonly used alpha-2 agonists for analgesia through intraperitoneal instillation route. The decreased opioid consumption postoperatively in dexmedetomidine and clonidine groups may emerge as one of the unique clinical regimens among the multimodal analgesia regimens in current clinical practice.

To conclude, the addition of alpha-2 agonists to bupivacaine intraperitoneally significantly reduces

Table 2: Comparison of pain (NRS scores) between study groups at different time intervals

Time	Group B	Group BD	Group BC	P
30 min	2.8±1.4	2.4±1.2	2.6±1.6	0.591
1 h	3.0±0.8	3.0±0.8	2.9±0.8	0.835
2 h	2.8±0.7	2.7±0.8	2.9±0.8	0.644
4 h	2.9±0.9	3.2±0.9	3.0±0.9	0.424
6 h	2.9±1.1	2.7±0.8	2.7±0.6	0.447
24 h	2.3±0.4	2.3±0.4	2.2±0.5	0.351

Group B: Bupivacaine, Group BD: Bupivacaine and dexmedetomidine, Group BC: Bupivacaine and clonidine. NRS: Numerical Rating Scale

Table 3: Comparison of the total amount of fentanyl given between study groups, mean time to first request for analgesia, the total number of times patient was given rescue analgesic

Variable	Group B	Group BD	Group BC	P
Total amount of fentanyl required (μ g) (Mean±SD)	35.7±40.0	16.8±29.0	15±26.4	0.016*
Time to first request for analgesia (min)	78.8±83.4	112.2±93.4	64.0±60.6	0.044*
Total number of times fentanyl was given n (%)				
1	15 (44.2%)	9 (27%)	9 (25.7%)	0.008
2	2 (5.8%)	0	0	

Group B: Bupivacaine, Group BD: Bupivacaine and dexmedetomidine, Group BC: Bupivacaine and clonidine

the amount of opioid consumption postoperatively without any significant reduction in pain intensity. Intraperitoneal dexmedetomidine along with bupivacaine provides a longer period of post-operative analgesia when compared to clonidine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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