Original Article

Analgesic efficacy of intra-peritoneal instillation of dexamethasone and bupivacaine versus bupivacaine following laparoscopic cholecystectomy – A randomised, double-blind controlled study

Address for correspondence:
Dr. Nanda Ananya,
3021, 3rd Floor OT Complex,
ESIC Medical College and
Hospital, Sanathnagar,
Hyderabad – 500 038,
Telangana, India.
E-mail: nanda.ananya@gmail.com

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Pakhare Vandana, Nanda Ananya, Muralikrishna D, Supraja Ponduru, Vyshnavi Renganathan, Ramchandran Gopinath
Department of Anaesthesia, ESIC Medical College and Hospital, Hyderabad, Telangana, India

ABSTRACT

Background and Aims: Laparoscopy is associated with acute pain. We compared the effectiveness of intra-peritoneal dexamethasone with bupivacaine versus bupivacaine in patients undergoing laparoscopic cholecystectomy for postoperative analgesia. **Methods:** This randomised study was conducted after approval from the institutional ethics committee and 84 patients were randomly allocated into bupivacaine with dexamethasone group (BD) (received 40 mL of 0.25% bupivacaine with 16 mg dexamethasone), and bupivacaine group (BB) (received 40 mL of 0.25% bupivacaine intra-peritoneally). Data analysis was done using R version 4.2.1. The visual analogue scale (VAS) score, total rescue analgesic dose, and time required for the first analgesic between groups were compared using the Wilcoxon rank sum test or *t*-test appropriately. **Results:** VAS score was significantly lower in the BD group compared to the BB group until 2 h post-operatively with a mean difference of – 1.0 (95% confidence interval [CI] –1.5, –0.53), $P < 0.001$. The total rescue analgesic dose consumed was lower in the BD group (60.71 mg [29.80]) compared to the BB group (73.20 mg [11.57]) with a mean difference of – 12.5 mg (95% CI – 22.3, –2.68), $P = 0.013$. In addition, the time taken for the requirement of the first rescue analgesic was significantly longer in the BD group (417.1 min [276.0]) compared to the BB group (219.4 min [226.1]) with a mean difference of 197.7 (95% CI 75, 320), $P = 0.002$. **Conclusion:** Intra-peritoneal instillation of 16 mg dexamethasone with 0.25% bupivacaine in laparoscopic cholecystectomy significantly reduces post-operative pain and requirement of rescue analgesic compared to 0.25% bupivacaine alone.

Keywords: Analgesia, bupivacaine, dexamethasone, intra-peritoneal, laparoscopy, pneumoperitoneum

INTRODUCTION

Laparoscopy has become the preferred mode for many diagnostic and operative procedures. It has the advantage of improved cosmesis, faster recovery, short post-operative hospital stays, and early resumption of normal activities.[1,2] Although the severity of pain after a laparoscopic procedure is less compared to laparotomy, but it is acute and can lead to increased analgesic requirements and prolonged hospital stays.[3] Several studies have evaluated post-laparoscopic pain relief methods such as intravenous analgesics, analgesic patches, steroids, and intra-peritoneal instillation of local anaesthetics alone or with additives

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such as morphine, dexmedetomidine, or steroids.[4,5] Intra-peritoneal injection of local anaesthetics such as lidocaine, ropivacaine, and bupivacaine has been used for post-laparoscopy pain relief. A single dose of dexamethasone injected intra-peritoneally has been reported to relieve pain after gynaecological laparoscopic surgery.[6]

We planned this randomised, double-blind clinical trial with the primary aim of comparing the effectiveness of intra-peritoneal dexamethasone with bupivacaine versus bupivacaine in patients undergoing laparoscopic cholecystectomy for postoperative analgesia. Secondary aims were comparing time to first rescue analgesic, total rescue analgesic dose, the occurrence of postoperative nausea, vomiting, hyperglycaemia, and any adverse effects among the groups.

METHODS

After approval from the institutional ethics committee (ESICMC/SNR/IEC-F269/05-2021, dated 08/06/2021) and trial registration in the Clinical Trials Registry- India (CTRI/2022/11/047379, www.ctri.nic.in/), this randomised double-blind clinical trial was conducted from 1 December 2022 to 31 March 2023 in accordance with the principles of the Declaration of Helsinki, 2013. Patients scheduled for laparoscopic cholecystectomy were evaluated for eligibility. All eligible participants were explained about the study, and written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. Eighty-four patients aged 18–60 years with American Society of Anesthesiologists (ASA) physical status I–II were recruited. Patients with diabetes mellitus, allergy to the study drug, patients on steroids, pregnant females, and patients with previous abdominal surgery were excluded from the study.

Patients were randomly allocated into two groups based on a computer-generated random table. The sequentially numbered sealed opaque envelope method was used for allocation concealment. The demographic characteristics, Apfel risk score for postoperative nausea and vomiting, and baseline blood sugar levels were noted. Patients were explained how to use a visual analogue scale (VAS), which consists of a 10-point scale representing varying pain intensity from 0 (no pain) to 10 (worst pain).

Peripheral venous access was secured on the day of surgery, and basic standard monitors were established. All patients received general anaesthesia with intravenous (IV) fentanyl 2 μg/kg, propofol 2–2.5 mg/kg, and vecuronium 0.1 mg/kg with endotracheal intubation. General anaesthesia was maintained using sevoflurane at 1–1.5 minimum alveolar concentration and IV fentanyl at 1 μg/kg dose if heart rate and systolic blood pressure increased by more than 20% of baseline. An additional dose of IV vecuronium (0.03 mg/kg) was administrated if required. During laparoscopy, the peritoneal cavity was insufflated with carbon dioxide to keep intra-abdominal pressure at 12–14 mmHg. Once pneumoperitoneum was confirmed, the study drug was administered intra-peritoneally through the umbilical port as per the patient randomisation. The bupivacaine with dexamethasone group (BD group) received 40 mL of 0.25% bupivacaine with 16 mg dexamethasone, whereas the bupivacaine group (BB group) received 40 mL of 0.25% bupivacaine. The drug was instilled with a 50-mL syringe attached to the umbilical port, following which the table was given a Trendelenburg position with a left-up tilt for 10 min for the drug to spread. After gas deflation, all patients received 1 g paracetamol IV infusion over 15 min and IV ondansetron 4 mg. At the end of the surgery, tracheal extubation was done after the reversal of residual neuromuscular blockade with IV neostigmine (50 μg/kg) and glycopyrrolate (8 μg/kg) with predefined criteria. Patients who required the insertion of drains and conversion to open cholecystectomy were excluded from the analysis. Patients and investigators collecting the post-operative data were blinded to the randomisation.

The primary outcome measure was the VAS pain score assessed by the VAS scale at 0, 1, 2, 4, 8, 12, 16, and 24 h post-operatively. The secondary outcome measures included time to first rescue analgesic, total rescue analgesic dose, occurrence of hyperglycaemia, post-operative nausea and vomiting, and adverse effects during the first 24 h post-operatively. The rescue analgesic, IV diclofenac 75 mg, was administered when the VAS score exceeded 3. The time to first rescue analgesic was measured in minutes, and the total rescue analgesic dose was noted in milligrams. Hyperglycaemia was defined as a blood sugar level of more than 200 mg/dL, measured using a point-of-care glucometer at 4 and 24 h post-operatively.

The sample size was calculated based on assumptions of a one-sided test assuming a lower VAS score in the

BD group compared to the BB group, a type-1 error rate of 5%, and a medium to large effect size of 0.55 from the literature.[7] The power was set at 80%. Using these assumptions, the required sample size was at least 42 participants per group. The data were analysed using R 4.2.1 software, developed and maintained by the R Core Team (Vienna, Austria). The program is open-source and freely available online (https://www.r-project.org/). Descriptive statistics for the numerical variable, such as time to rescue analgesic and VAS score, were presented using the mean and standard deviation (SD) or median with interquartile range when not normally distributed. Categorical variables such as age, sex, and Apfel score were presented as frequency and percentage. Comparison among the two groups was done using the Wilcoxon rank sum test or *t*-test for numerical variables and the Chi-square test or Fisher's exact test for nominal variables. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Eighty-eight patients were screened for eligibility, and 84 patients were randomly allocated to the two groups, with 42 patients in each group [Figure 1]. The demographic characteristics and distribution of patients in ASA physical status I and II, baseline blood sugar level, and Apfel score were comparable among the study groups [Table 1]. The VAS score was significantly lower in the BD group compared to the BB group till 4 h post-operatively [Table 2]. The mean (SD) time for the requirement of the first dose of rescue analgesic was significantly more in the BD group (417.1 [276.0] min) compared to the BB group (219.4 [226.1] min) with a mean difference of 197.7 (95% confidence interval [CI] 75,320) min, $P = 0.002$. The mean (SD) total rescue analgesic consumed in 24 h post-operatively was significantly less in the BD group (60.71 [29.80] mg) compared to the BB group (73.20 [11.57] mg) with a mean difference of − 12.5 (95% CI − 22.3, −2.68) mg, $P = 0.013$ [Table 3]. In addition, both groups showed no evidence of hyperglycaemia at 4 and 24 h post-operatively [Table 3]. None of the patients experienced nausea, vomiting, or adverse drug effects till 24 h post-operatively.

DISCUSSION

Our study found that the VAS score for pain was significantly lower in the BD group compared to the BB group until 2 h following laparoscopic cholecystectomy.

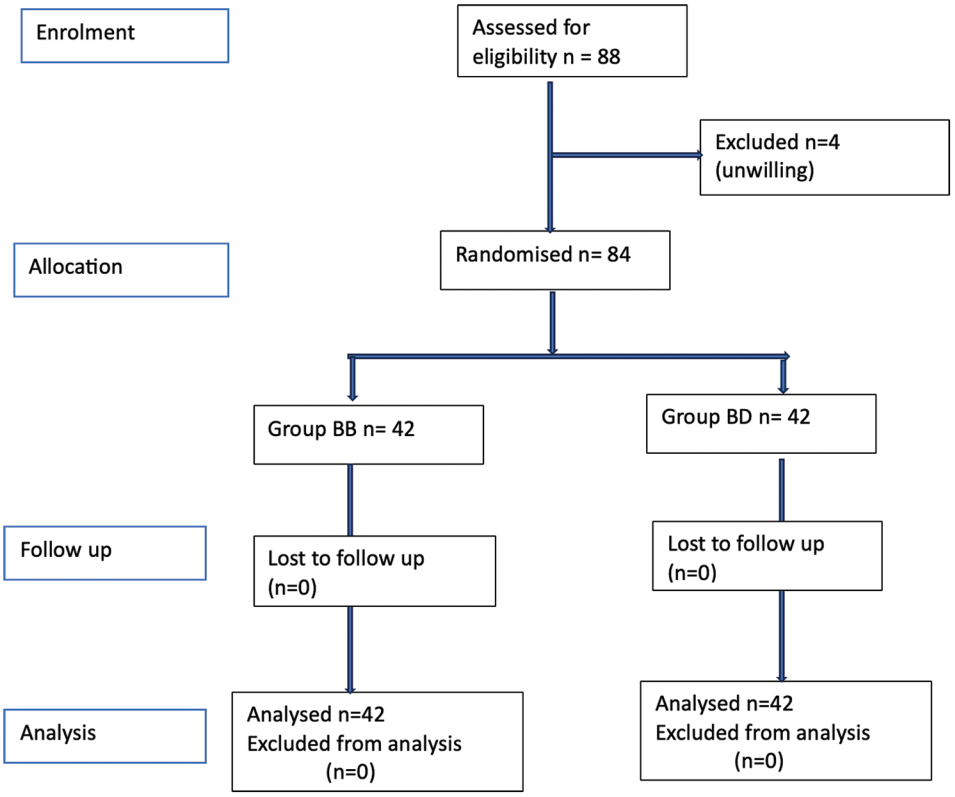

Figure 1: Consolidated standards of reporting trials (CONSORT) flow of participants. n: Number of patients, BB group=Bupivacaine only; BD group=Bupivacaine with dexamethasone

Laparoscopic procedures are minimally invasive but are associated with high-intensity acute pain in the early postoperative period.[8-10] Sharma *et al*.[7]. reported that after laparoscopic cholecystectomy, the VAS score was significantly lower in the intra-peritoneal bupivacaine hydrocortisone group than in bupivacaine alone at 0, 2, 4, 6, 12, and 24 h post-operatively, with $P < 0.05$ at all the time points. This prolonged analgesic effect can be attributed to the ability of steroids in decreasing pain through their anti-inflammatory property, suppressing neuropeptide and bradykinin release and inhibiting inflammatory mediators such as tumour necrosis factor (TNF) and interleukins.[11,12] Asgari *et al*.[6] also reported that intra-peritoneal instillation of 16 mg dexamethasone significantly reduces post-laparoscopic pain until 24 h post-operatively compared to placebo ($P < 0.001$).

In our study, participants in the bupivacaine dexamethasone group required rescue analgesic doses significantly later than bupivacaine alone. This finding aligns with the observation made by Nasr *et al*.[13], who reported that patients receiving intra-peritoneal bupivacaine with 8 mg dexamethasone had a significantly longer duration of analgesia 9.2 h (0.14) as compared to bupivacaine alone 6.1 h (0.19) following laparoscopic bariatric surgery.

In our study, the total rescue analgesic dose needed was significantly less in the BD group. Similar findings were noted by Nasr *et al*.,[13] who reported that patients receiving intra-peritoneal bupivacaine with dexamethasone consumed significantly less rescue analgesic 3.4 mg (2.8) compared to bupivacaine alone 15.2 mg (7.5) with $P < 0.001$ following laparoscopic bariatric surgery. Similarly, Srivastava *et al*.[14] also observed that the requirement of rescue analgesia was significantly less in patients who received intra-peritoneal dexamethasone–dexmedetomidine combination compared to individual drugs alone ($P < 0.001$) during laparoscopic gynaecological procedures. These findings align with our result, which concludes that adding dexamethasone enhances and prolongs the analgesic effect of intra-peritoneal bupivacaine.

Steroid-induced hyperglycaemia is one of the main adverse effects. The risk of development of hyperglycaemia is higher with the systemic route and depends on the dose used, patient age, baseline body mass index, and history of diabetes.[15] In our study, both group patients' blood glucose levels were within normal limits till 24 h post-operatively. None of the patients from both groups reported nausea or vomiting.

In several animal studies, intra-peritoneal instillation of dexamethasone has also been shown to prevent adhesion post-operatively.[16] Further research is needed in humans on the evaluation of this potential benefit of adhesion prevention.

One of the limitations of our study was that we included only ASA I and II patients; the effect of intra-peritoneal dexamethasone in ASA class III and

Table 1: Demographic characteristics

	BB group (*n*=42)	BD group (*n*=42)
Age (years)	35 (11.2)	35.5 (12.0)
Sex (Female/Male)	31/11	35/7
Weight (kg)	60.0 (11.9)	60.0 (8.7)
ASA (I/II)	22/20	27/15
Baseline blood sugar (mg/dL)	123.1 (31.2)	113.2 (26.1)
Apfel score (I/II)	14/28	19/23

Data are expressed as mean (standard deviation) or numbers. ASA=American Society of Anesthesiologists physical status class, BB group=Bupivacaine, BD group=Bupivacaine with dexamethasone, n=Number of patients

Table 2: Visual analogue scale (VAS) score at different time intervals in 24 h post-operatively

Post-operative time (h)	BD group (*n*=42)	BB group (*n*=42)	Mean difference (95% CI)	*P*
0	2.0 (1.8)	3.4 (2.6)	−1.4 (−2.4, −0.49)	0.004
1	1.7 (1.4)	2.8 (1.5)	−1.1 (−1.7, −0.44)	0.001
2	1.7 (1.0)	2.7 (1.2)	−1.0 (−1.50,−0.53)	<0.001
4	1.9 (1.1)	2.4 (1.4)	−0.44 (−0.99, 0.11)	0.110
8	2.6 (1.6)	2.5 (1.6)	0.06 (−0.63, 0.75)	0.900
12	2.1 (1.2)	1.7 (1.2)	0.35 (−0.16, 0.86)	0.200
16	1.7 (1.0)	1.3 (1.2)	0.44 (−0.03, 0.91)	0.069
24	1.1 (0.6)	0.9 (1.1)	0.19 (−0.20, 0.58)	0.300

Data are expressed as mean (standard deviation); BB group=Bupivacaine only; BD group=Bupivacaine with dexamethasone; CI=Confidence interval

Table 3: Comparison of random blood sugar, time to first rescue analgesic, and total dose of rescue analgesic

Parameters	BD group (*n*=42)	BB group (*n*=42)	Mean difference (95% CI)	*P*
Random blood sugar 4 h (mg/dL)	127.5 (29.9)	131.8 (31.6)	−4.4 (−18, 8.9)	0.500
Random blood sugar 24 h (mg/dL)	140.0 (154.8)	118.4 (19.6)	22 (−27, 70)	0.400
Time to first rescue analgesia (min)	417.1 (276.0)	219.4 (226.1)	197.7 (75, 320)	0.002
Total dose of rescue analgesic (mg)	60.71 (29.80)	73.21 (11.57)	−12.5 (−22.31, −2.68)	0.013

Data are expressed as mean (standard deviation); BB group=Bupivacaine only; BD group=Bupivacaine with dexamethasone; CI=Confidence interval, n=Number of patients

IV patients with uncontrolled diabetes mellitus needs to be evaluated. In addition, we did not follow patients beyond 24 h.

CONCLUSION

Intra-peritoneal instillation of 16 mg dexamethasone with 0.25% bupivacaine in laparoscopic cholecystectomy significantly reduces post-operative pain and requirement of rescue analgesic compared to 0.25% bupivacaine alone.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared upon request.

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Conflicts of interest

There are no conflicts of interest.

ORCID:

Vandana Patilbuwa Pakhare: https://orcid.org/0000-0003-0158-9921

Ananya Nanda: https://orcid.org/0000-0002-8401-2062

Supraja Ponduru: https://orcid.org/0000-0003-2240-6784

Vyshnavi Renganathan: https://orcid.org/0000-0002-0864-2492

Ramchandran Gopinath: https://orcid.org/0000-0002-5782-3716

Murali Krishna Dommeti: https://orcid.org/0009-0002-7280-4289

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