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CLINICAL RESEARCH

Paravertebral block using levobupivacaine or dexmedetomidine-levobupivacaine for analgesia after cholecystectomy: a randomized double-blind trial

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Abstract

Background: Thoracic paravertebral block (TPVB) has emerged as an effective and feasible mode of providing analgesia in laparoscopic cholecystectomy. Though a variety of local anaesthetic combinations are used for providing TPVB, literature is sparse on use of dexmedetomidine in TPVB. We aimed to compare levobupivacaine and levobupivacaine-dexmedetomidine combination in ultrasound guided TPVB in patients undergoing laparoscopic cholecystectomy.

Methodology: 70 ASA I/II patients, aged 18–60 years, scheduled to undergo laparoscopic cholecystectomy under general anaesthesia were enrolled and divided into two groups. Before anaesthesia induction, group A patients received unilateral right sided ultrasound guided TPVB with 15 ml 0.25% levobupivacaine plus 2 ml normal saline while group B patients received unilateral right sided ultrasound guided TPVB with 15 ml 0.25% levobupivacaine plus 2 ml solution containing dexmedetomidine 1 $\mu g.kg^{-1}$. Patients were monitored for pain using Numeric Rating Scale (NRS) at rest, on movement, coughing and comfort scores post surgery. Total analgesic consumption in first 48 hour postoperative period, time to first request analgesic and pain scores were recorded.

Results: Total amount of rescue analgesia (injection tramadol plus injection tramadol intravenous equivalent dose) consumed during 48 hours postoperatively in group A was 146.55 mg while in group B was 111.30 mg ($p = 0.026$). Mean time for demanding rescue analgesia was 273 minutes in group A while in group B was 340 minutes ($p = 0.00$).

Conclusion: TPVB using dexmedetomidine 1 $\mu g.kg^{-1}$ added to levobupivacaine 0.25% in patients undergoing laparoscopic cholecystectomy significantly reduced total analgesic consumption in first 48 hours and provided longer duration of analgesia postoperatively compared to levobupivacaine 0.25% alone.

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Introduction

Laparoscopic cholecystectomy is one of the most commonly performed surgeries in gall ball disease patients. A large number of patients undergoing laparoscopic cholecystectomy may suffer from severe postoperative pain if analgesia is not managed appropriately.[1] The presence of acute postoperative pain causes extreme patient discomfort, extended post-anesthesia care unit stays and restricts early recovery that should have been seen in laparoscopic surgeries. Over the past years, paravertebral blocks (PVB) have been increasingly used for providing postoperative analgesia.[2] The use of ultrasound in the administration of thoracic paravertebral block has greatly reduced the incidence of associated complications.[3] There are reports in literature describing the use of TPVB for providing post-laparoscopic cholecystectomy analgesia.[4,5] Though a variety of local anesthetics have been used for administering TPVB, there is scarcity of studies on adjuvants in thoracic paravertebral block in laparoscopic cholecystectomy. Hence the present trial was designed to assess additional analgesic requirement in patients undergoing laparoscopic cholecystectomies after preoperative unilateral thoracic PVB using two different analgesic combinations (levobupivacaine *vs.* levobupivacaine and dexmedetomidine combination). We hypothesized that adding dexmedetomidine to levobupivacaine would reduce the postoperative analgesic consumption and increase the time to first rescue analgesic.

Methodology

Ethics

After obtaining approval from the institutional ethics committee of Post Graduate Institute of Medical Education and Research, Chandigarh (9171/INT/IEC/PG-2Trg/2012/22034), dated November 20, 2013, this prospective, randomized, double-blind trial was carried out by the Department of Anesthesia & Intensive Care and Department of General Surgery of the institute.

Inclusion and exclusion criteria

After obtaining written informed consent, 70 ASA (American Society of Anesthesiologists) I/II patients, aged 18–60 years, scheduled to undergo laparoscopic cholecystectomy under general anesthesia were enrolled in the study. Patients with history of allergy to local anesthetics, coagulopathy, morbid obesity and having decreased pulmonary reserve, cardiac disorders, renal dysfunction, pre-existing neurological deficits, psychiatric illness were excluded from the study.

Randomization

Patients were randomized using coded sealed envelopes computer generated, and subsequently participants were allocated to one of the two groups of 35 patients each. In group A, patients received unilateral right-sided ultrasound guided thoracic paravertebral block with 15 ml 0.25% levobupivacaine plus 2 ml normal saline, while in group B, patients received unilateral right-sided ultrasound guided thoracic paravertebral block with 15 ml 0.25% levobupivacaine plus 2 ml solution containing dexmedetomidine 1 $\mu g.kg^{-1}$.

Blinding

Both the participants and the investigators were blinded to the medications used for the PVB until the completion of study. All the investigators involved in patient's management and data collection, including the patient's anesthesiologist giving general anesthesia, were unaware of the group assignment.

Procedure

In the preoperative room, patients were monitored for heart rate (HR), blood pressure (BP), continuous electrocardiogram (ECG) and arterial oxygen saturation (SpO_2) using standard monitors. Baseline readings were recorded, and an intravenous access was established in all patients. All the patients were premedicated with intravenous midazolam 25 $\mu g.kg^{-1}$, ranitidine 1 $mg.kg^{-1}$ and palanosetron 1 $\mu g.kg^{-1}$. To perform the block, patients were placed in sitting position and spinous process of T8 vertebra was identified and marked. Under aseptic precautions, using a sterile high-frequency (5–10 MHz) ultrasound probe (Sonosite, Inc. Bother. Wa 98021 USA), the thoracic paravertebral space was identified.[6] After infiltrating the skin with 3–5 ml of 1% lignocaine, in-plane needle guidance technique was followed using a 20G epidural needle on unilateral right side. Once the tip of the needle was in a position between the internal intercostal membrane and the pleura, the study drug was administered, after negative aspiration over a period of 30 seconds. During administration of the local anesthetic, downward displacement of the parietal pleura was observed. Patient's hemodynamics were monitored for a period of 20 minutes after giving the block. Following this, patients were shifted to operating room. In the operating room, patients were monitored for heart rate (HR), blood pressure (BP), continuous electrocardiogram (ECG), arterial oxygen saturation (SpO2), end-tidal carbon dioxide ($ETCO_2$) and temperature using multichannel monitors (Datex-Ohmeda S/5 Avance). General anesthesia in all the participants followed a standard anesthetic technique. After preoxygenation with 100% oxygen, anesthesia was induced with injection fentanyl 1.5 $\mu g.kg^{-1}$ and propofol 2–3 $mg.kg^{-1}$. Atracurium 0.5 $mg.kg^{-1}$ was given to facilitate tracheal intubation. The maintenance of anesthesia was provided with oxygen and isoflurane. The patients received top-ups of intravenous atracurium (0.1 $mg.kg^{-1}$) at regular intervals using TOF.[7] Heart rate and mean arterial pressure were maintained within 20% of the baseline values by the administration of additional bolus doses of fentanyl (0.5 $\mu g.kg^{-1}$), if required, and the amount of additional intravenous fentanyl consumed intraoperatively was noted. At the end of surgery, 500 ml normal saline was used for the intraperitoneal irrigation in all the patients, and residual neuromuscular blockade was reversed with injection neostigmine 50 $\mu g.kg^{-1}$ and injection glycopyrrolate 10 $\mu g.kg^{-1}$, and local anesthetics

were not infiltrated in trocar sites. On return of consciousness and adequate recovery of muscle strength, patients were extubated and shifted to the postanesthetic care unit (PACU).

Follow-up

In the postoperative room, patients were monitored for mean arterial pressure (MAP), pulse rate (PR), NRS[8] (0 for no pain and 10 for worst imaginable pain) for parietal pain, visceral pain, and shoulder pain – during rest, on movement and on coughing, nausea or vomiting and sedation at regular intervals (30 minutes, 60 minutes, 1–4 hours, 4–12 hours, 12–24 hours, 24–48 hours) – by an investigator blinded to group allocation. Patients were also assessed for the comfort score,[9] where 0 is the least comfortable and 10 is the most comfortable. If at any time interval patients comfort score was < 6, the intensity of parietal and visceral pain at rest (supine), on movement (sitting up from supine), on coughing and shoulder pain were noted. Rescue analgesia (intravenous injection tramadol 1.5 $mg.kg^{-1}$) was given if comfort score was < 6. If the pain persisted even after 30 minutes of intravenous tramadol administration, then intravenous injection morphine sulphate 0.1 $mg.kg^{-1}$ (second rescue analgesic agent) was given. Time from extubation of the patient to the administration of first dose of rescue analgesic was noted. Total 48 hours intravenous (IV) morphine consumption was converted to IV tramadol equivalent dose and total 48 hours rescue analgesia consumption (IV tramadol plus IV tramadol equivalent dose) during the postoperative period were noted. We also recorded the total number of patients requiring rescue analgesia. Sedation was assessed using sedation score from 0 to 5 (responds readily – 5, lethargic response – 4, responds only after name is called loudly – 3, responds only after mild prodding or shaking – 2, does not respond to mild prodding or shaking – 1, does not respond to noxious stimulation – 0).[10] Nausea and vomiting were assessed in postoperative care unit by PONV score.[11] If the patient complained of severe nausea or an episode of vomiting, rescue antiemetic in the form of injection 10 mg metoclopramide was given intravenously. If it still persisted after giving injection metoclopramide, 4 mg of injection ondansetron was given as second rescue antiemetic. Side effects like shivering, pruritus, nausea/vomiting, dizziness, respiratory depression were noted during the study period. Any patient who failed to understand these scoring systems was excluded from the study design.

Primary and secondary outcomes

The primary outcome was to measure the total analgesic consumption in the first 48 hours postoperative period. The secondary outcome was defined as the time to first request for rescue analgesic, pain scores and side-effects in the postoperative period.

Statistical analysis

The data was analyzed with Statistical Package for Social Studies (SPSS – SPSS for Windows 14, Chicago, IL, USA). The parametric data (age, height, weight) were analyzed using the independent samples *t*-test, while the non-parametric data were analyzed using Mann-Whitney U test. Continuous data like heart rate and blood pressure were analyzed by repeated measure ANOVA after checking the normal distribution. Within group analysis of hemodynamic data was done using post-hoc analysis. The occurrence of postoperative emetic episodes, rescue antiemetic therapy and rescue analgesic therapy was analyzed with Chi-square test or Fisher Exact test where appropriate. Data were stated as mean ± standard deviation (SD), median (25–75%) values or number (n) and percentage (%). A *p*-value of < 0.05 was considered statistically significant.

Sample size calculation

Considering the 20% difference in the consumption of analgesic drug between the two groups with a power of 80% and confidence interval of 95%, 33 patients were required in each group.[11] However, considering the possibility of dropouts, we decided to enroll 35 patients in each group.

Results

A total number of 70 patients scheduled for laparoscopic cholecystectomy were included in this prospective, randomized study. They were divided into two groups (A and B) with 35 patients each (Figure 1). Baseline demographic parameters in both groups were comparable (Table 1). Intraoperative parameters were also comparable in both groups (Table 2). The preoperative, intraoperative and postoperative hemodynamic parameters did not differ significantly between the two groups ($p > 0.05$) (Figure 2).

Primary outcome

The total amount of rescue analgesia (injection tramadol plus injection tramadol intravenous equivalent dose) consumed during the 48 hours postoperatively in group A was 146.55 mg, which was significantly higher than in group B (111.30 mg; $p = 0.026$).

Secondary outcome

The mean time for demanding rescue analgesia was significantly more in group B than in group A (group A was 273 minutes and group B was 340 minutes; $p = 0.00$). The number of patients who required first rescue analgesia (injection tramadol IV) was the same in both the groups, but the number of patients requiring second rescue analgesia (injection morpine IV) differed significantly. In group A, 13 out of 35 patients required a second rescue analgesia, while in group B 5 out of 35 patients required second rescue analgesia ($p = 0.029$). There was no significant difference in the intraoperative fentanyl consumption (group A = 106.98 μg; group B = 92.80 μg; $p = 0.26$)

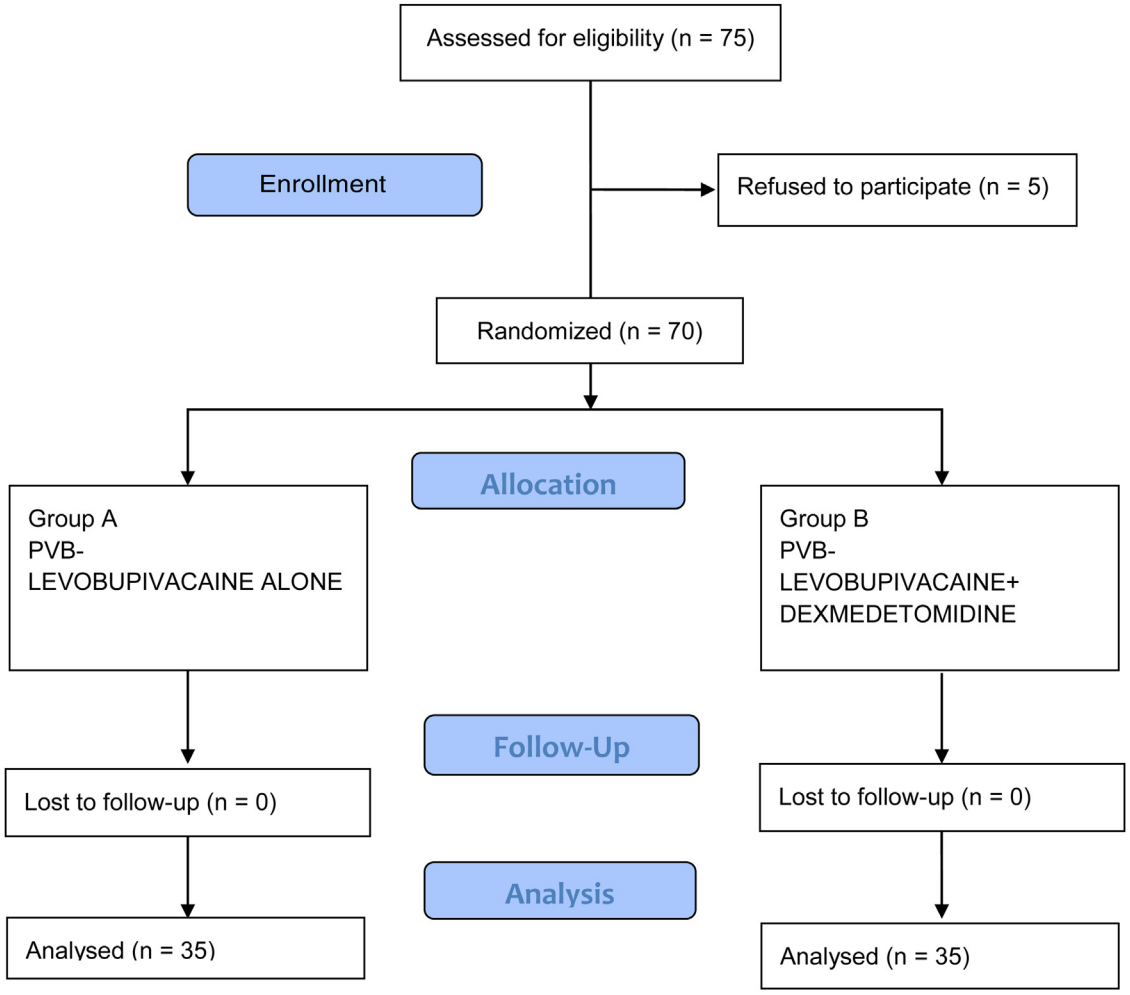

Figure 1 Consort diagram.

Table 1 Demographic features of study population.

Parameters	Group A (Mean ± SD)	Group B (Mean ± SD)	*p*-value
Age (years)	41.23 ± 12.262	40.17 ± 10.001	0.694
Sex (female/male)	27/8	25/10	0.584
Height (cm)	158.17 ± 4.586	157.20 ± 3.932	0.345
Weight (kg)	62.77 ± 10.241	60.71 ± 9.096	0.377
ASA (I / II)	22/13	27/8	0.192
Surgery time	61.07 ± 15.2	58 ± 10.95	0.757
Average fentanyl (μg)	106.98 ± 11.58	92.8 ± 13.03	0.265

Values are expressed as mean ± SD or absolute numbers. ASA, American Society of Anesthesiologists physical status.

Table 2 Intraoperative variables in both the groups were comparable ($p > 0.05$).

Intraoperative variables	Group A (Mean ± SD)	Group B (Mean ± SD)	*p*-value
Duration of surgery (min)	68.67 ± 14.87	70.31 ± 15.16	0.328
Duration of anesthesia (min)	83.56 ± 16.82	86.22 ± 17.99	0.268
Total fentanyl dose (μg)	106.98 ± 11.58	92.80 ± 13.03	0.265
Intra-abdominal pressure	13.47 ± 0.991	13.89 ± 1.385	0.518

Values are expressed as mean ± SD or absolute numbers.

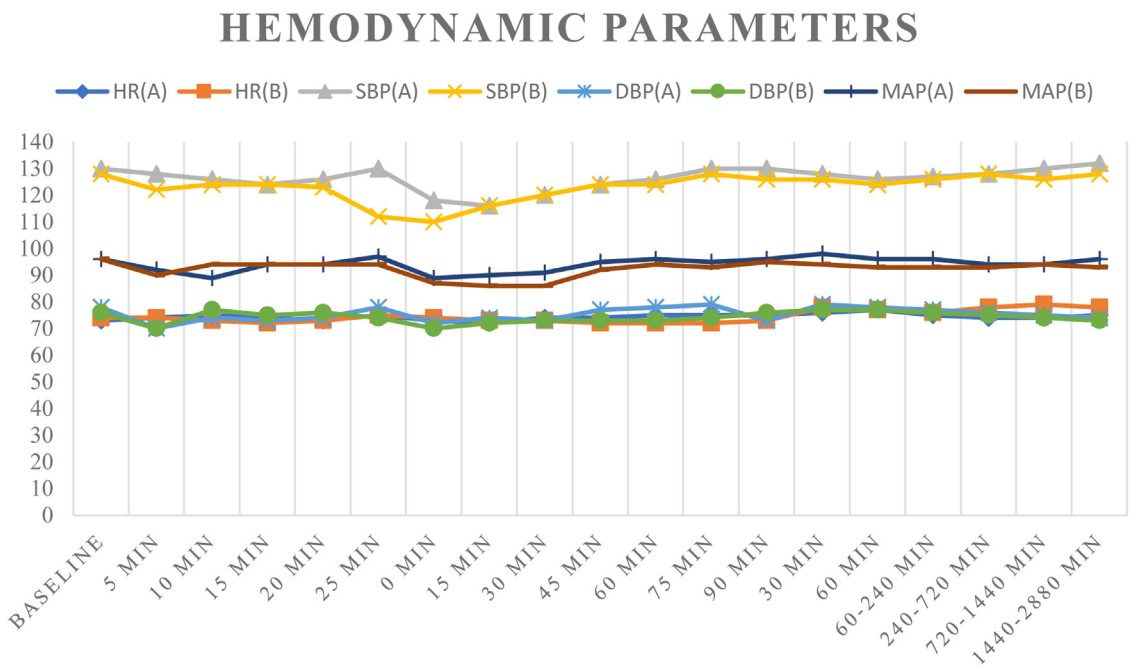

Figure 2 Hemodynamic parameters in the preoperative (0–25 min), intraoperative period (0–90 min) and postoperative period (30–2880 min).
HR(A), Heart Rate group A; HR(B), Heart Rate group B; SBP(A), Systolic Blood Pressure group A; SBP(B), Systolic Blood Pressure group B; DBP(A), Diastolic Blood Pressure group A; DBP(B), Diastolic Blood Pressure group B; MAP(A), Mean Arterial Pressure group A; MAP(B), Mean Arterial Pressure group B.

Comfort score

There was no difference in comfort score between the groups during 30 minutes, 60 minutes, 720–1440 minutes, 1440–2880 minutes time interval (comfort score > 6 in both groups). During 60–240 minutes interval, the number of patients whose comfort score was < 6 in group A was 11, and in group B was 5. But during the 240–720 minutes time interval, all the patients in both groups had comfort score < 6. However this difference was not statistically significant (p = 0.08) (Figure 3).

NRS for parietal and visceral pain

At 60–240 minutes, NRS scores for parietal pain, as well as visceral pain – at rest, on movement and on coughing – were less in group B compared to group A; however this difference was statistically insignificant (Table 3, Figure 4). But during the 240–720 minutes interval, the NRS scores for parietal pain at rest, on movement and on coughing was significantly less in group B compared to group A (Figure 5). During this time, visceral pain scores were almost the same in both groups. We did not assess NRS during 30, 60, 720–1440, 1440–2880 minutes, as the comfort score during this period was > 6 in all the patients.

Shoulder pain

In both groups there was no difference in the number of patients complaining of shoulder pain. Three patients in each group complained of shoulder pain in the postoperative period.

Sedation score

In the postoperative period, the sedation score was significantly low in patients belonging to group B, as compared to those in group A at 30 minutes (p = 0.000) and at 60 minutes (p = 0.001) (Figure 6).

PONV

There was no significant difference between the two groups in the incidence of PONV and usage of rescue antiemetic. Out of 35 patients in each group, 8 patients in group A and 3 patients in group B complained of nausea in immediate postoperative period, and one patient in group A had an episode of vomiting.

Adverse effects

Postoperatively in group A, one patient had an episode of hypotension and one patient had an episode of bradycardia, which was resolved later with IV crystalloids. While in group B two patients had an episode of hypotension which was resolved with IV crystalloids and one patient had an episode of severe episode of bradycardia for which required intervention (injection of atropine 0.6 mg was given). None of the patients in our study reported chest pain or breathlessness, indicative of pneumothorax.

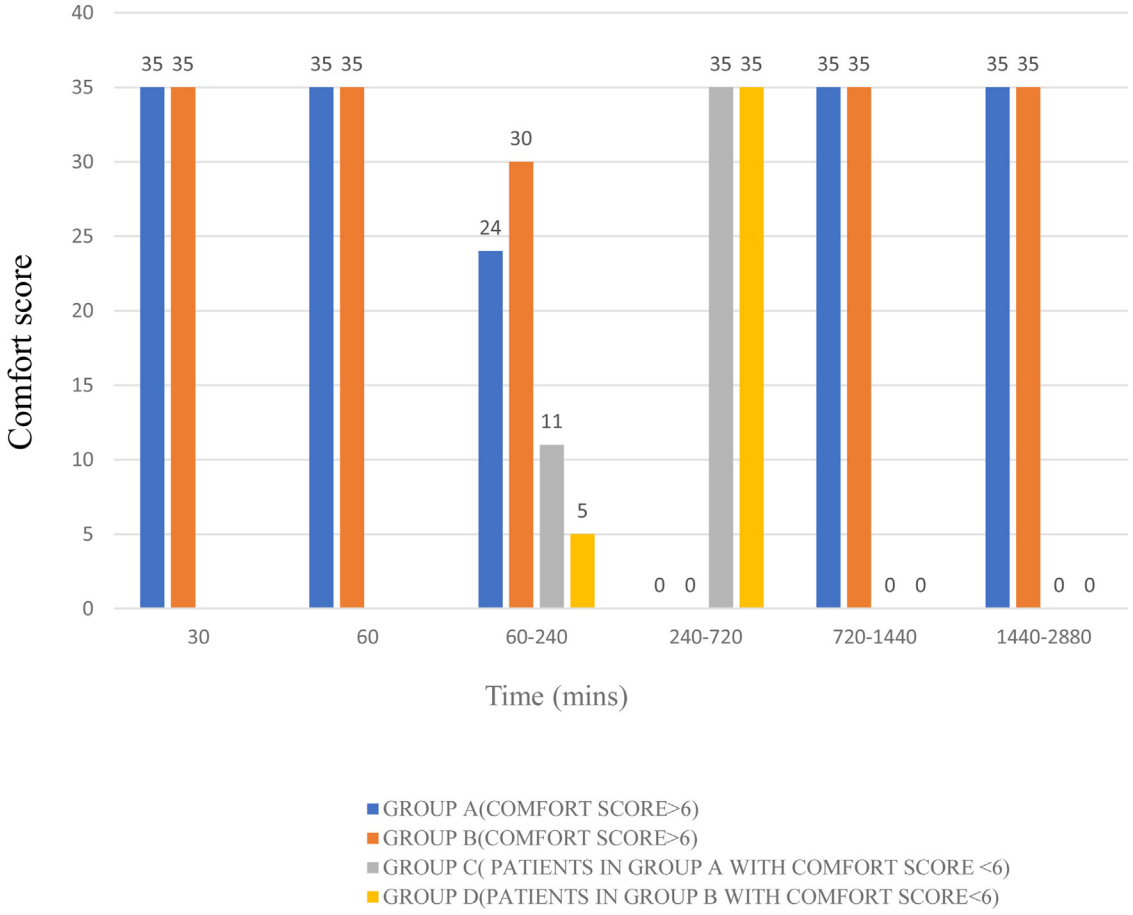

Figure 3 Comfort score (30–2880 min).

Table 3 NRS during 60–240 min interval.

NRS	Group A (n = 35) (Mean ± SD)	Group B (n = 35) (Mean ± SD)	*p*-value
PP NRS R	3.91 ± 0.831	3.40 ± 0.548	0.235
PP NRS M	4.64 ± 0.924	4.20 ± 0.837	0.384
PP NRS C	5.45 ± 0.688	4.80 ± 0.837	0.120
VP NRS R	3.36 ± 0.505	3.00 ± 0.000	0.136
VP NRS M	4.18 ± 0.751	3.80 ± 0.447	0.314
VP NRS C	5.00 ± 0.632	4.60 ± 0.548	0.244

PP NRS R, Parietal pain Numeric Rating Scale at Rest; PP NRS M, Parietal Pain Numeric Rating Scale at Movement; PP NRS C, Parietal Pain Numeric Rating Scale while coughing; VP NRS R, Visceral Pain Numeric Rating Scale at Rest; VP NRS M, Visceral Pain Numeric Rating Scale at Movement; VP NRS C, Visceral Pain Numeric Rating Scale while coughing.
Values are expressed as mean ± SD or absolute numbers.

Discussion

The main finding of this prospective, randomized double-blind trial was the significant improvement in analgesic efficacy of dexmedetomidine and levobupivacaine combination as compared to levobupivacaine alone in PVB in patients undergoing laparoscopic cholecystectomy. Postoperative analgesic consumption was reduced during the entire 48 hours postoperative observation period in patients who received a combination of levobupivacaine and dexmedetomidine in PVB. Furthermore, the pain scores both at rest and in movement were less in these patients, and the time to first rescue analgesic was also significantly more. In addition, patients receiving combination of levobupivacaine and dexmedetomidine had lower incidence of PONV, less sedation scores and better patient comfort score.

Laparoscopic cholecystectomy is now being increasingly performed on an outpatient basis, and hence effective analgesia with opioid-sparing attributes is being preferred to hasten postoperative recovery. Laparoscopic cholecystectomy is associated with a substantial component of visceral pain, and the incidence of shoulder pain probably reflects a component of diaphragmatic referred pain.[12] The risk of chronic postoperative pain has been reported to be 10–40%

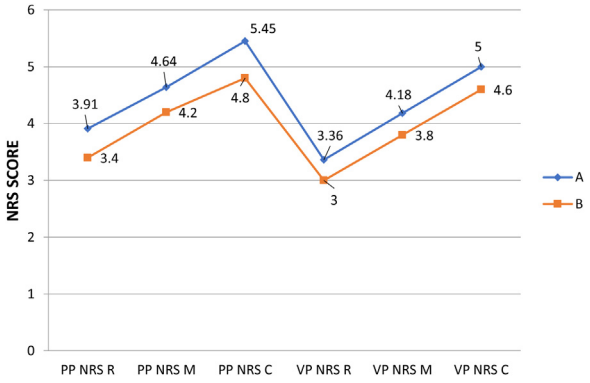

Figure 4 NRS during 60–240 min interval. A, group A; B, group B.
PP NRS R, parietal pain numeric rating scale at rest; PP NRS M, parietal pain numeric rating scale on movement; PP NRS C, parietal pain numeric rating scale on coughing; VP NRS R, visceral pain numeric rating scale at rest; VP NRS M, visceral pain numeric rating scale on movement; VP NRS C, visceral pain numeric rating scale on coughing.

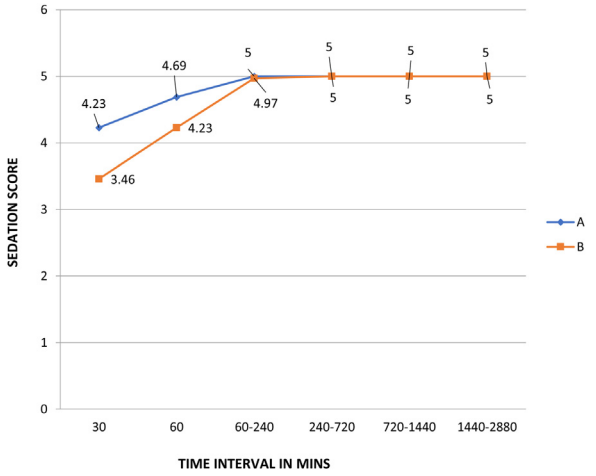

Figure 6 Sedation score was significantly low in patients belonging to Group B, as compared to those in Group A at 30 min ($p = 0.000$) and at 60 min ($p = 0.001$).

after laparoscopic or traditional open cholecystectomy.[13] Thus, in order to provide adequate pain relief, both high quality afferent somatic and visceral pain blockade are most likely necessary in order to successfully treat cholecystectomy pain. Paravertebral blockade has been reported to provide high quality afferent blockade with abolishment of somatosensory evoked potentials,[14] and it has also been found capable of attenuating the postoperative stress response associated with traditional cholecystectomy. Naja et al. assessed the efficiency of nerve stimulator guided bilateral paravertebral blockade (with a combination of lignocaine, bupivacaine, fentanyl and clonidine) combined with general anesthesia *vs.* general anesthesia alone in reducing postoperative pain following laparoscopic cholecystectomy.[4] They found that when used as a complement to general anesthesia, paravertebral blockade with lidocaine, bupivacaine, fentanyl and clonidine improved postoperative pain relief. Aggarwal et al., in their study demonstrating the efficacy of paravertebral block using bupivacaine in laparoscopic cholecystectomy, showed that patients receiving PVB required 38% less PCA morphine compared to those in the control group. Intraoperative supplemental fentanyl requirement in their study group was 54% less than the control group.[11] Junior et al., in their meta-analysis, have compared thoracic epidural with paravertebral block for postoperative pain in patients undergoing thoracotomy and found no statistically significant difference in pain relief between thoracic epidural and paravertebral block, though paravertebral block was associated

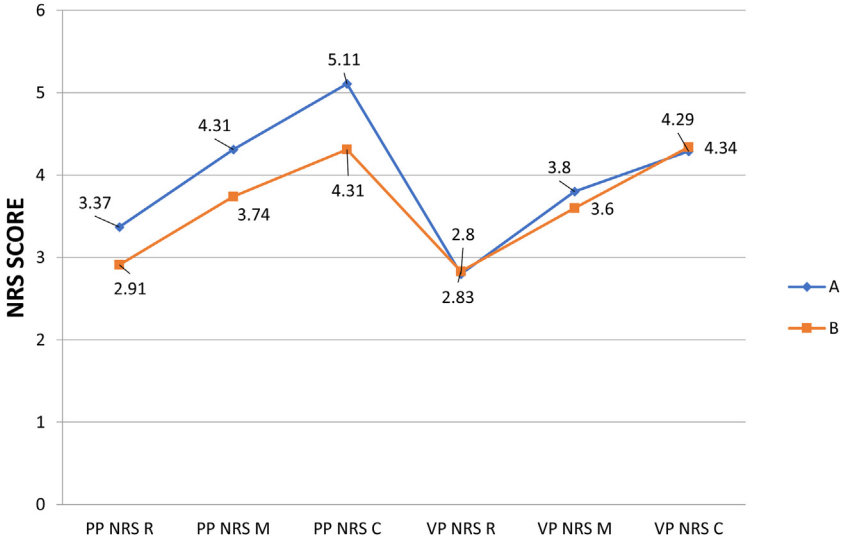

Figure 5 NRS during 240–720 min interval. A, group A; B, group B.
PP NRS R, parietal pain numeric rating scale at rest; PP NRS M, parietal pain numeric rating scale on movement; PP NRS C, parietal pain numeric rating scale on coughing; VP NRS R, visceral pain numeric rating scale at rest; VP NRS M, visceral pain numeric rating scale on movement; VP NRS C, visceral pain numeric rating scale on coughing.

with significantly less incidence of hypotension and urinary retention.[15]

Dexmedetomidine has emerged as a potential adjuvant exhibiting a facilitatory effect with LA.[16] Numerous studies have been reported in literature where dexmedetomidine has been used as adjuvant to local anesthetics for peripheral nerve blockade.[17–24] In most of them, it has shown improved efficacy of the block with no reports of neurological side-effects. The efficacy of paravertebral block using local anesthetics with or without opioids has also been shown in previous studies.[25] However, none of the studies reported so far has evaluated the role of dexmedetomidine along with local anesthetics for giving thoracic PVB in laparoscopic cholecystectomy. In the present study, PVB was given to both groups, but used different combinations of drugs (levobupivacaine – dexmedetomidine/levobupivacaine) for administering the block, and found that the combination of levobupivacaine and dexmedetomidine when used for giving paravertebral block in laparoscopic cholecystectomy resulted in significant decrease in postoperative pain, as compared to using levobupivacaine alone.

PONV is one of the most unpleasant symptoms perceived by the patients following laparoscopic cholecystectomy. Kehlet et al.[26] have extensively reviewed opioid-sparing effects of different regimens and remarked that approximately 30% reduction in opioid requirement was clinically significant. An opioid-sparing analgesic technique should also result in decreased incidence of opioid-related side effects. Hence, we compared the occurrence of opioid-related adverse effects,[27] like dizziness, nausea, vomiting, constipation, and respiratory depression between the two groups. In our study, patients in group B reported less PONV than those in the group A in the postoperative period. The number of patients who complained of PONV and who required rescue antiemetic was 3 out of 35 patients in group B postoperatively, as compared to 8 out of 35 patients in the study group A. This difference reflects significant opioid-sparing benefit of PVB in terms of reduced PONV, but did not attain statistical significance, presumably due to the small sample size.

In the postoperative period, sedation score was significantly low in patients belonging to group B, as compared to those in group A at 30 minutes (p = 0.000) and at 60 minutes (p = 0.001). This could have been due to the addition of dexmedetomidine to levobupivacaine for giving PVB in patients of group B. In a study by Jung HS et al.,[28] who compared the effect of intraoperative infusion of dexmedetomidine with remifentanil on perioperative hemodynamics, hypnosis, sedation, and postoperative pain control, the authors found that sedation score was significantly lower in the dexmedetomidine group than in the remifentanil group after arrival in the PACU. This is because dexmedetomidine has sedative and analgesia-sparing effects via central actions in the locus coeruleus and in the dorsal horn of the spinal cord. It inhibits noradrenaline release, causing an attenuation of excitation in the central nervous system, especially in the locus coeruleus.[29]

Although this is first study comparing analgesic efficacies of levobupivacaine and levobupivacaine-dexmedetomidine combination for PVB block in laparoscopic cholecystectomy, our study has some limitations. We have not evaluated sensory block distribution and drug concentrations in the blood. Another limitation is the lack of pneumoperitoneal insufflation pressure recordings. There is some evidence that maintaining low inflation pressures during laparoscopic surgery may reduce postoperative pain.[30]

Conclusion

The present study concluded that the administration of ultrasound guided TPVB using dexmedetomidine 1 $\mu g.kg^{-1}$ added to levobupivacaine 0.25% in patients undergoing laparoscopic cholecystectomy significantly reduced the total analgesic consumption in the first 48 hours and provided longer duration of analgesia postoperatively, as compared to levobupivacaine 0.25% alone.

Conflicts of interest

The authors declare no conflicts of interest.

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