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Intraperitoneal Instillation of Dexmedetomidine vs Dexamethasone as Adjuvant to Bupivacaine for Postoperative Pain in Laparoscopic Cholecystectomy, a Randomized Clinical Trial

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Abstract

Background: Intraperitoneal instillation (IPI) of local anesthesia was reported to reduce postoperative pain after laparoscopic surgeries. We aim to evaluate the effectiveness of IPI of bupivacaine + dexmedetomidine versus bupivacaine + dexamethasone on postoperative pain in patients undergoing laparoscopic cholecystectomy (LC). **Methods:** This randomized clinical trial was carried out on one hundred patients who underwent LC under general anesthesia. Patients were randomly divided into: **Group (Dexa):** IPI of bupivacaine with dexamethasone and **Group (Dexmed):** IPI of bupivacaine with dexmedetomidine. **Results:** The first time to request analgesia was significantly delayed in the dexmed group (P value < 0.001). The total analgesic consumption in the 1st postoperative day significantly increased considerably when using IPI of dexmedetomidine as an adjuvant to Bupivacaine (P value < 0.001). VAS, HR, and MAP at 2 h postoperative were statistically but not clinically significantly higher in the dexamethasone group (P value < 0.001), while there were no significant differences at 1, 4, 8, 16, and 24 h postoperative. **Conclusions:** Intraperitoneal Bupivacaine + Dexmedetomidine provided longer pain-free postoperative duration lower pain score over time, and lesser analgesic consumption.

Keywords

Bupivacaine, Dexmedetomidine, Dexamethasone, Laparoscopic

Cholecystectomy

1. Introduction

The most common surgical procedure for cholelithiasis is laparoscopic cholecystectomy (LC). The most common surgical procedure for cholelithiasis is laparoscopic cholecystectomy (LC). Compared to open surgery, laparoscopic surgeries provide several benefits, including less bleeding, improved cosmetic outcomes, less discomfort following surgery, and a quicker recovery period, which results in a shorter hospital stay and lower costs. [1]

Pain is a complex multifactorial phenomenon. As a result, the combination of several analgesic methods and drugs that operate on various target locations may provide exceptional dynamic pain relief with fewer side effects. Just regional bupivacaine has a brief half-life. The local anesthetic (LA) analgesia can be prolonged with the application of adjuvants. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) was effective. Steroid administration showed promise. When compared to LA alone, dexmedetomidine perineural injection extended motor block and lengthened the duration of the first analgesic request. [2]

Sedation, analgesia, anxiolysis, and sympatholytic are all provided by the $\alpha 2$-adrenergic agonist effect of Dexmedetomidine. There are theories that dexmedetomidine provides natural sleep like sedation with almost no respiratory affection. [3] It is found that usage of dexmedetomidine improves postoperative pain and reduces postoperative analgesic usage. [4]

Adding dexmedetomidine as an adjuvant to bupivacaine was found to enhance the overall outcomes, which is explained by the different mechanisms of action of each, as bupivacaine works by blocking Na channels, while Dexmedetomidine reduces the perception of pain by reducing polarization of spinal cord neurons. [5]

When dexamethasone and bupivacaine are administered intraperitoneally during laparoscopic cholecystectomy, post-operative discomfort and the need for rescue analgesics are greatly decreased. [6] Post-laparoscopic pain management techniques have been studied in the literature, such as steroids, and intra-peritoneal instillation (IPI) of LA. [6]

We aim to compare the effectiveness of IPI of bupivacaine + dexmedetomidine versus bupivacaine + dexamethasone on postoperative pain in patients undergoing LC.

2. Patients and Methods

This trial was carried out on 100 patients who underwent LC under general anesthesia aged ≥ 18 old with ASA I or II. Patients signed an informed consent before participating in the study. We conducted our research within the timeframe between May 2024 and December 2024 after approval of Ethical Committee Aswan University Hospitals, Aswan, Egypt has been issued (approval code: 917/5/24) and

registration of clinicaltrials.gov (ID: NCT06535256) was done. Our team got signed informed consent from all cases. Exclusion criteria were patients with/on diabetes mellitus (DM), study drug allergies, steroids, pregnant, and/or cardiac, pulmonary, hepatic, or renal disorders.

Randomization: Patients were allocated into 2 groups.

Group (Dexa): IPI of bupivacaine + dexamethasone (40 mL of 0.25% bupivacaine + 16 mg dexamethasone + 5 ml normal saline).

Group (Dexmed): IPI of bupivacaine with dexmedetomidine (40 mL of 0.25% bupivacaine + dexmedetomidine 1 μg/kg + normal saline 5 ml).

The numeric Visual Analogue Scale (VAS) score for pain was explained to all patients pre-operatively. The score was explained to the patient as follows: 0 when there is no pain, and 10 is the worst pain ever experienced. After arrival in the operating room, routine monitors were applied (ECG, NIBP, and pulse oximetry), and an 18-gauge IV cannula was inserted. The patient was pre-medicated with ondansetron injection (150 μg/kg) and fentanyl injection (2 μg/kg) IV. Then he/she was oxygenated through a face mask with 100% oxygen for 3 min. We used IV propofol 2 mg/kg and IV atracurium 0.5 mg/kg in the induction. Then the patient was intubated with a cuffed endotracheal tube. During the operation, controlled ventilation was used with 100% O_2, isoflurane (1% - 2%), and atracurium maintenance dose.

Intraoperative monitoring included NIBP, SpO_2, ECG, and end-tidal carbon dioxide ($ETCO_2$). Regarding the surgical technique, we then used either 3 or 4-port techniques under direct visual access to the peritoneum. $ETCO_2$ was maintained between 35 - 40 mm of Hg and intra-peritoneal pressure was between 12 - 14 mm of Hg. Intraoperatively, patients were administrated normal saline, ringer lactate, and dextrose at the rate of 5 - 7 ml/kg/hr.

At the end of the surgical procedure, the Surgeon was under direct vision, and 45 ml of intervention was instilled before the removal of the trocar.

IV atropine 0.01 mg/kg and IV neostigmine 0.05 mg/kg were used to reverse the neuromuscular blockade. Then we extubate patients after proper suctioning. Patients were then moved to the recovery room. After maintaining spontaneous breathing, obeying verbal commands, and being vitally stable, the patient moved to the ward. When the VAS pain score ≥ 4, IV diclofenac sodium (75 mg slowly) is used as a rescue analgesic with a maximum dose of 150 mg in 24 hours.

We studied the following variables:

1) Time to first seek for analgesia (first time to request analgesia after extubation).

2) Overall analgesic dose on the first postoperative day (POD).

3) Incidence and severity of postoperative pain for 1st POD using VAS pain score at 1, 2, 4, 8, 16, and 24 h postoperatively.

4) Hemodynamics (heart rate and mean arterial blood pressure at 1, 2, 4, 8, 16, and 24 h postoperatively.

5) Postoperative complications.

Sample Size Calculation

Sample size was calculated by G power software version 3.1.3 program based on data from a previous study, according to previously published study [2]. With the (two-sided) α error set at 0.05 and the β error set at 0.2 (power of 80%), the time to first request of analgesia, the median & IQR in study groups was 7 (4 - 12) hours and in other group was 4 (2 - 8) hours. By meta-analysis accelerator/calculate the mean & SD from median & IQR (meta-cnoverter.com), the Mean ± SD was 7.70 ± 6.23 in one group and 4.67 ± 4.67 in other group the sample size was 106 cases (53 patients in each group). We decided to recruit 73 patients per group and added 20 patients to each group to avoid drop out cases, so the sample size was 146 patients, 73 in each group.

Statistical Analysis

Statistical analysis was done using SPSS v26 (IBM Inc., Armonk, NY, USA). To assess the normality of the data, we used histogram, kurtosis, skewness, and normality tests (Shapiro-Wilks's test and Kolmogorov Smirnov test). Normally distributed data was analyzed using an independent t-test, while not normal data was analyzed using Mann-Whitney. Categorical data was analyzed using Chi-square test. A two-tailed P value ≤ 0.05 was considered statistically significant.

3. Results

One hundred forty-six cases underwent an eligibility assessment to be involved in our research and assessment for analyzing research cases, was illustrated on the consort flow diagram (**Figure 1**). 46 were excluded (28 cases did not meet the inclusion criteria, 18 cases refused to participate). The final sample was 100 cases that were enrolled in this study and randomized to be included in one of the two equal study groups (n = 50) with no loss to follow-up cases.

We included 100 patients, and 58% of them were males and 50% were ASA I. The demographics between the two groups were insignificantly different between the two studied groups. (**Table 1**)

The time to first request analgesia was significantly longer in dexmed group compared to dexa group (P value < 0.001). The total dose of analgesia in the first 24 hours was statistically significantly higher in dexa group (P value < 0.001). (**Table 2**)

Post-operative pain after 2 and 24 h postoperative was significantly higher in dexa group (P value <0.001 and 0.007 respectively), while the pain was comparable throughout the first POD. (**Table 3**, **Figure 2**)

At 2 and 24 h postoperative, there were statistically but clinically significant differences in HR between the two groups (P value = 0.005 and 0.045, respectively). (**Table 4**, **Figure 3**)

MAP at 2 and 24 h postoperative was statistically significantly higher in group dexa group (P value = 0.017 and 0.036, respectively). (**Table 5**, **Figure 4**)

The difference in incidence of postoperative complications wasn't statistically significant between the two studied groups. (**Table 6**)

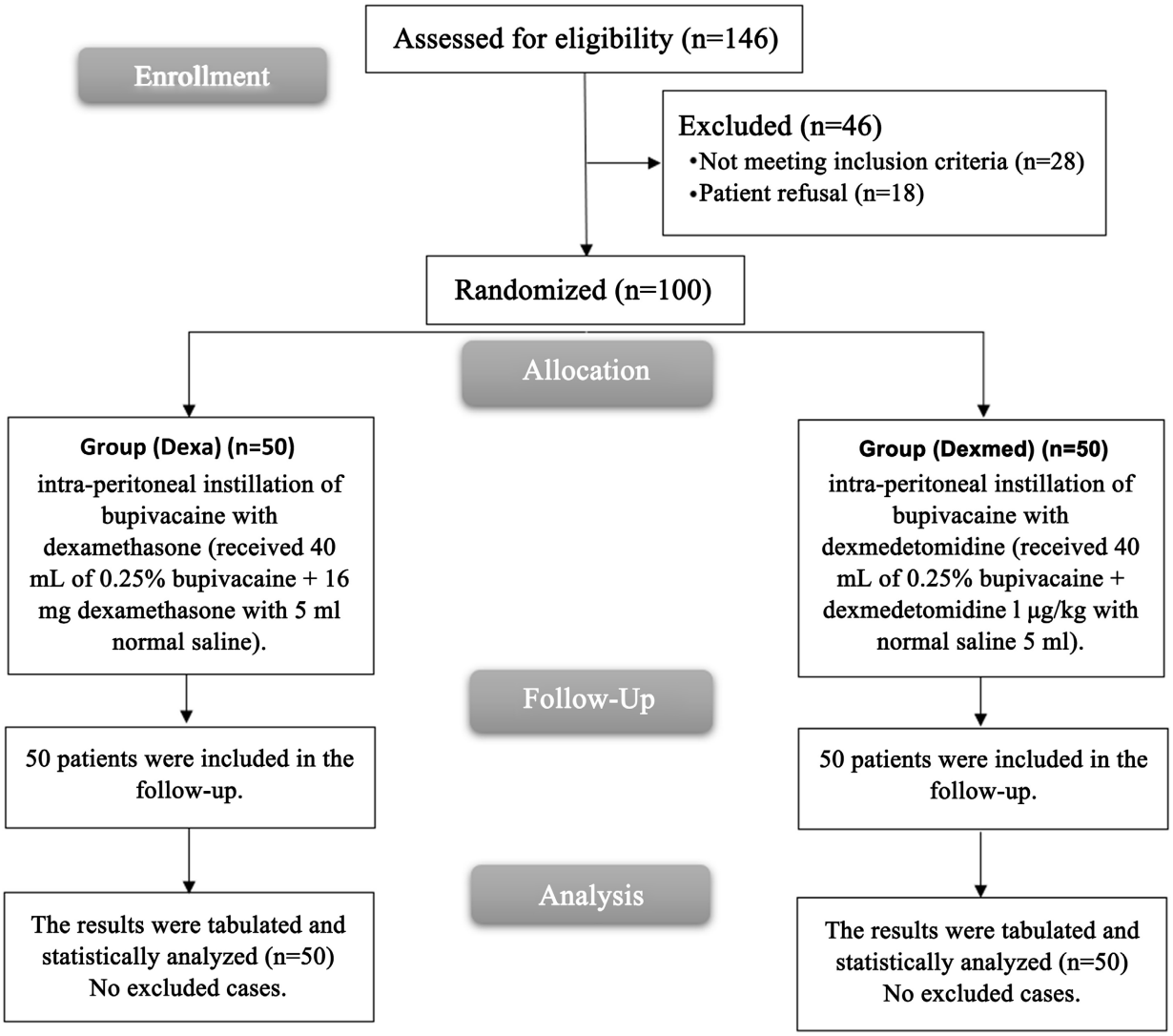

Figure 1. CONSORT flow chart.

Table 1. Demographic data of the studied groups.

		Group (Dexa) (n = 50)	Group (Dexmed) (n = 50)	P value
Age (years)		39.72 ± 11.4	40.5 ± 11.62	0.735
BMI (kg/m^2)		25.18 ± 4.21	25.76 ± 4.1	0.488
Sex	Male	26 (52%)	32 (64%)	0.224
	Female	24 (48%)	18 (36%)	
ASA	I	27 (54%)	23 (46%)	0.424
	II	23 (46%)	27 (54%)	
Duration of surgery (min)		55.6 ± 7.8	56 ± 6.55	0.782

BMI: Body mass index, ASA: American Society of Anaesthesiologists. (P value was determined by t-test to compare the difference in mean and Chi-square to compare the differences in frequencies between groups).

Table 2. Analgesic performance of the studied groups.

	Group (Dexa) (n = 50)	Group (Dexmed) (n = 50)	P value
Time to first request of analgesia (h)	2.84 ± 1.0	5.92 ± 2.02	<0.001*
Total analgesic dose in the first POD (mg)	132 ± 32.36	100.5 ± 35.89	<0.001*

(P value was determined by t-test to compare the difference in mean). *: significant as P value ≤ 0.05.

Table 3. Pain score (VAS) of the studied groups.

	Group (Dexa) (n = 50)	Group (Dexmed) (n = 50)	P value
1 h	2 (1 - 2)	2 (1 - 3)	0.710
2 h	5 (2 - 6)	2 (2 - 3)	<0.001*
4 h	3 (3 - 6)	4 (2 - 6)	0.671
8 h	2 (2 - 3)	2.5 (1 - 4)	0.134
16 h	3 (2 - 4.75)	2 (1.25 - 3)	0.053
24 h	3 (2 - 6)	2 (1 - 3)	0.007*

(P value was determined by Mann-Whitney to compare the difference in VAS). *: significant as P value ≤ 0.05.

Table 4. Postoperative HR of the studied groups.

	Group (Dexa) (n = 50)	Group (Dexmed) (n = 50)	P value
1 h	78.72 ± 13	78.44 ± 11.7	0.910
2 h	87.18 ± 15.72	79.08 ± 11.93	0.005*
4 h	85.26 ± 14.85	84.18 ± 15.01	0.718
8 h	84.76 ± 13.41	82.38 ± 12.62	0.363
16 h	84.76 ± 13.57	83.38 ± 11.67	0.587
24 h	87.82 ± 12.22	82.78 ± 12.57	0.045*

Data are presented as mean ± SD. HR: heart rate. (P value was determined by t-test to compare the difference in mean). *: significant as P value ≤ 0.05.

Table 5. Postoperative MAP of the studied patients.

	Group (Dexa) (n = 50)	Group (Dexmed) (n = 50)	P value
1 h	78.88 ± 9.06	80.68 ± 8.91	0.319
2 h	86.46 ± 11.53	81.38 ± 9.31	0.017*
4 h	84.2 ± 10.62	83.8 ± 11.55	0.857
8 h	84.38 ± 9.85	83.22 ± 9.52	0.551
16 h	84.56 ± 9.03	84.5 ± 10.77	0.976
24 h	86.72 ± 9.13	82.78 ± 9.44	0.036*

MAP: mean arterial blood pressure. (P value was determined by t-test to compare the difference in mean). *: significant as P value ≤ 0.05.

Table 6. Postoperative complications of the studied patients.

	Group (Dexa) (n = 50)	Group (Dexmed) (n = 50)	P value
Nausea	7 (14%)	4 (8%)	0.525
Vomiting	4 (8%)	2 (4%)	0.678
Pruritis	0 (0%)	0 (0%)	---

(P value was determined by Chi-square to compare the difference in frequencies). *: significant as P value ≤ 0.05.

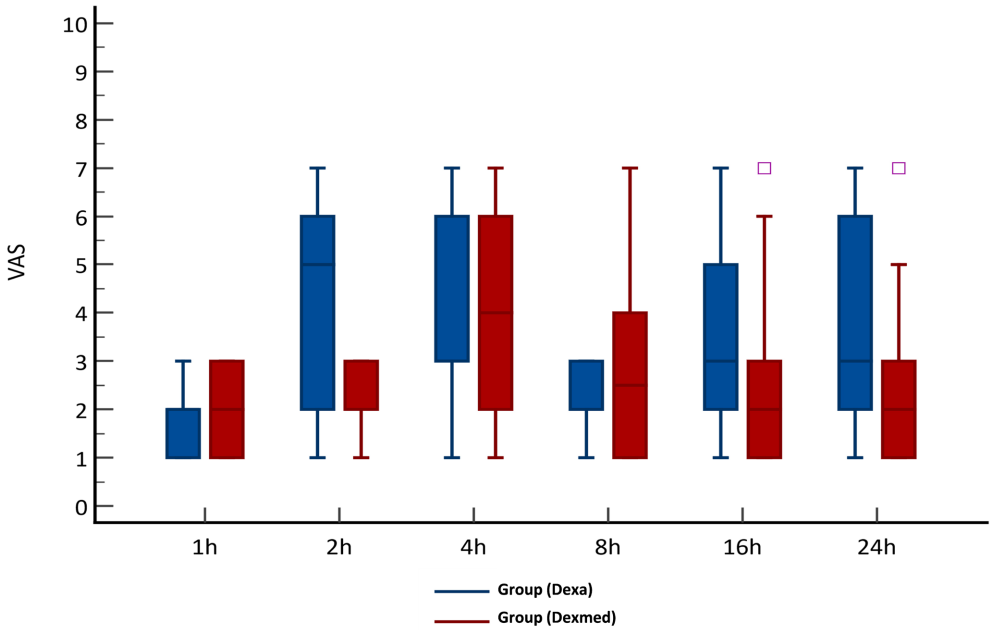

Figure 2. VAS of the studied patients.

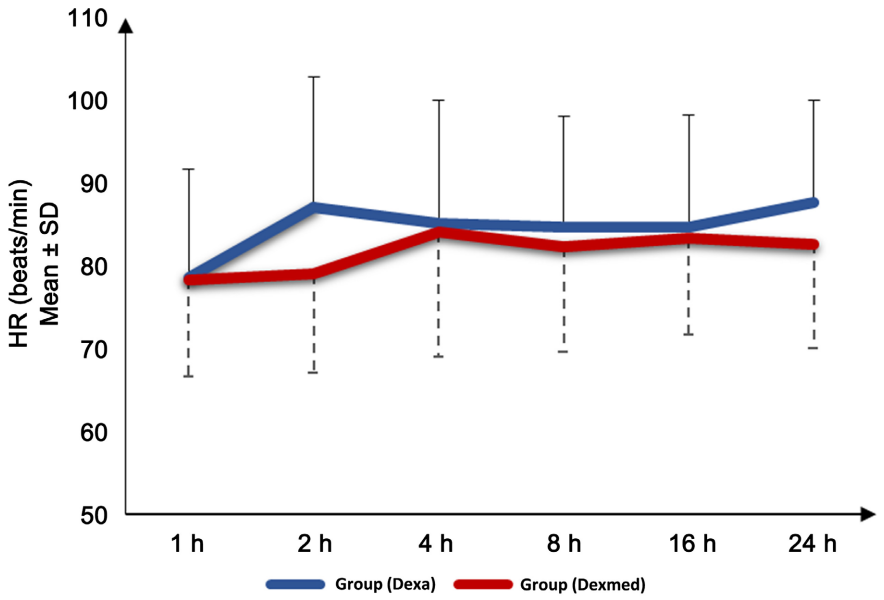

Figure 3. Postoperative HR of the studied patients.

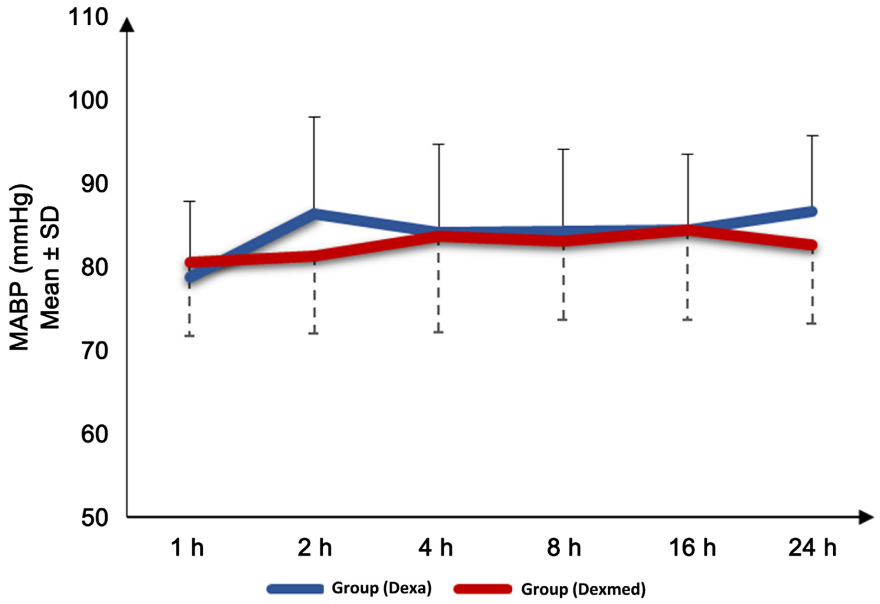

Figure 4. Postoperative MABP of the studied patients.

4. Discussion

LC is the standard of care for cholelithiasis. Laparoscopy is superior to open surgery in terms of shorter recovery time and post-operative pain, which decreases post-operative hospital stays and lowers the cost [1]. However, LC isn't a pain-free procedure [7]. The pain can be attributed to expansion due to pneumoperitoneum, and irritation of the phrenic nerve if the CO_2 was used in the insufflation and the incision [7] [8].

Intraperitoneal installation is usually used to block the visceral pain route [9]. Bupivacaine alone is short-lived, and the literature showed the superiority of using bupivacaine +adjuvant over using bupivacaine alone [10]. Dexmedetomidine perineural administration showed promising results compared with LA alone [2]. Moreover, IPI of dexamethasone as an adjuvant to bupivacaine in LC showed a significant reduction in pain control and analgesic usage [6].

Our study showed that there were no significant differences regarding demographics. The time to first request for analgesia was significantly longer in the dexmedetomidine group, while the total dose of analgesia in the first POD was significantly higher dexamethasone group. Postoperative pain at 2 and 24 h was significantly higher when we used dexamethasone. There were no clinical hazards in terms of Hemodynamics in either group. However, there were statistically significant differences. The incidence of postoperative complications was insignificantly different between the two studied groups. As there is no significant difference regarding the baseline characteristics, we attribute the differences to the effect of adding Dexmedetomidine.

The time to first request analgesia was significantly delayed in the dexmedetomidine group, indicating better and longer pain relief when using it as an adjuvant. Shankar *et al.* found that using Dexmedetomidine as an adjuvant found

to increase the time to first request analgesia compared to bupivacaine alone [9].

Chetan & Raksha [11] found that the duration to require the first dose of analgesia was longer in the dexmedetomidine group as compared to bupivacaine alone. In bariatric surgery, Nasr *et al.* [12] found that the time to first supplementary analgesia was longer when using dexamethasone compared to bupivacaine alone. Moreover, Shukla *et al.* [1] concluded that the time to first request analgesia (min) in the bupivacaine+ dexmedetomidine group was longer than the Group bupivacaine alone or plus tramadol. De Pace *et al.* [13] show the efficacy of intraperitoneal installation of local anesthetics in the pediatric population undergoing laparoscopic surgeries.

The total analgesic usage in the first POD was significantly higher in the dexamethasone group. Several studies' results were similar to our findings. Shankar *et al.* found that Dexmedetomidine was found to significantly decrease consumption of analgesia in the first POD compared to bupivacaine alone [9].

In gynecological laparoscopy, Srivastava *et al.* [14] found that analgesic requirement is comparable between dexmedetomidine and dexamethasone while there were significant reductions when compared to bupivacaine alone. Chetan & Raksha found that the total dose of analgesic was lower in the dexmedetomidine group compared to bupivacaine alone [11].

Shukla *et al.* [1] reported that the total analgesic dose (mg) was the lowest bupivacaine + dexmedetomidine. Nasr *et al.* [12] found that the total analgesic dose in the first POD was the lowest when using dexamethasone as an adjuvant to bupivacaine.

Using intraperitoneal installation of local anesthetics was found to be effective across different populations, age groups and different laparoscopic abdominal procedures, and adding dexmedetomidine was found to enhance the bupivacaine effect. The superiority of dexmedetomidine can be due to the effect on α2a and α2c adrenoceptors in the spinal cord, and by affecting the descending pathways [5] [15].

Postoperative pain at 2 and 24 h postoperative was significantly higher in dexamethasone. Sharma *et al.* [16] reported significantly lower pain after using intraperitoneal steroids as adjuvants to bupivacaine compared to no adjuvants in LC, while Asgari *et al.* [17] show lower pain after gynecologic laparoscopy. Shukla *et al.* [1] reported that overall pain in the first POD was significantly lower dexmedetomidine group.

In a study by Fares *et al.* [15] bupivacaine + dexmedetomidine enhances postoperative analgesia duration and quality. Additionally, Shankar *et al.* [9] reported lower VAS scores during the 1st 24 hours postoperative when using Dexmedetomidine compared to bupivacaine with tramadol or bupivacaine alone. Nasr *et al.* [12] reported lower numbers of patients requiring supplementary analgesia in the dexamethasone group. Srivastava *et al.* [14] have observed better analgesia in patients receiving dexmedetomidine compared with dexamethasone.

There were no clinical hazards regarding hemodynamics in either group.

However, there were statistically significant differences. The study of Chetan & Raksha [11], Bhattacharjee *et al.* [18] and Arain *et al.* [19] showed similar results to our findings.

The incidence of postoperative complications was insignificantly different between the two studied groups. Srivastava *et al.* [14] found that postoperative nausea and vomiting (PONV) significantly reduced when using either dexmedetomidine or dexamethasone compared to normal saline. Nasr *et al.* [12] reported that PONV was lower in the dexamethasone group.

Our results suggest that Dexmedetomidine and dexamethasone are safe options with no reported complications. Moreover, both drugs were reported to be used as a prophylaxis and therapeutic for PONV [20].

According to our knowledge, this is the first trial to compare the IPI of dexmedetomidine and dexamethasone as an adjuvant to bupivacaine in LC.

Intraperitoneal administration of Bupivacaine with Dexmedetomidine is a safe option that should be adopted in laparoscopic procedures, as it provides longer pain-free duration, lower pain score over time, less analgesic consumption and lower overall costs.

Limitations

The study was conducted on one type of abdominal surgery. We didn't evaluate the effect on chronic postsurgical pain, so studies with longer follow-up times are recommended. Further studies should be conducted on other types of abdominal surgeries and other populations.

5. Conclusion

Intraperitoneal administration of Bupivacaine with Dexmedetomidine showed better outcomes compared to Bupivacaine with Dexamethasone as it provided longer pain-free postoperative duration, lower pain score over time, and less analgesic consumption. Meanwhile, both interventions were shown to be safe, with no hemodynamic or postoperative complications in laparoscopic cholecystectomy.

Contribution

All authors actively contributed to data collection, literature review, and writing. Mohammed S. Aly performed the statistical analysis.

Conflicts of Interest

No conflict of interest.

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