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A comparative study of the analgesic efficacy of intraperitoneal instillation of diluted bupivacaine versus non-diluted bupivacaine after laparoscopic cholecystectomy, a prospective single-blinded controlled randomized study

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ABSTRACT

Intraperitoneal (IP) bupivacaine instillation for postoperative analgesia after laparoscopic cholecystectomy (LC) has been reported in many studies as either diluted or non-diluted, with conflicting results and no standard recommendations.

Objective: Our study aims to compare the analgesic efficacy of intraperitoneal instillation of diluted versus non-diluted bupivacaine after laparoscopic cholecystectomy.

Methods: In this prospective, single-blinded, controlled and randomized study, we included 50 patients undergoing LC. They were randomly divided into two groups, with 25 patients each. At the end of surgery, the first group received intraperitoneal 20 ml bupivacaine 0.5% (100 mg), added to 480 ml normal saline, diluted bupivacaine group (DBG) and the second group received intraperitoneal 20 ml bupivacaine 0.5% (100 mg); non-diluted bupivacaine group (NBG). Pain was assessed and recorded using the visual analog scale (VAS) for 24 h. Time to the first analgesic request, total analgesic consumption in 24 h, incidence of negative effects after LC, such as nausea, vomiting and shoulder pain, any side effects due to local anesthetic used as hypotension, bradycardia or respiratory depression and hemodynamic parameters were also recorded.

Results: Postoperative VAS values were significantly lower in DBG than NBG in the 1st 24 h (P value ≤ 0.003). The duration of analgesia (the 1st time analgesic request) was significantly longer in DBG (20.16 ± 3.52 h) than that in NBG (6.19 ± 2.93 h) (P value = 0.0001). Also, the total amount of postoperative analgesic consumption (tramadol) was less in DBG (7.2 ± 19.9 mg) than NBG (63 ± 31.16 mg) (P value = 0.0001). In relation to negative effects after LC, side effects due to analgesic drugs and hemodynamic parameters, the results were comparable in both groups.

Conclusion: Intraperitoneal instillation of diluted bupivacaine at the end of laparoscopic cholecystectomy decreases postoperative pain, delays request for rescue analgesia and reduces the amount of analgesics in the 1st 24 h postoperatively, more than non-diluted bupivacaine, with comparable results in incidence-negative effects after LC, side effects due to analgesic drugs and comparable hemodynamic parameters.

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Diluted bupivacaine; intraperitoneal; laparoscopic cholecystectomy; analgesia

1. Introduction

Gallstones are thought to affect 10–15% of the general population, with some regional variations [1]. The gold standard for treating gallstone disease with symptoms is LC in the great majority of patients [1,2]. Pain is the leading complaint and the main cause of extended convalescence after LC in 17–41% of the patients. Also, pain is the main reason for patients to stay overnight in the hospital on the day of operation which is especially crucial because many centers are doing LC on a day-case basis. Furthermore, there is a theory that suggests that severe acute pain following an LC could indicate the onset of persistent pain, such as post-laparoscopic cholecystectomy syndrome [3,4]. The most common complaint following LC is still postoperative pain in addition to negative side effects related to LC such as nausea, vomiting, and shoulder pain. Adequate pain management promotes early walking, lowers the risk of deep vein thrombosis and pulmonary embolism, improves the patient's capacity for deep breathing to lower the risk of pulmonary complications (such as pneumonia and atelectasis), and lowers the incidence of tachycardia and unwarranted tests associated with it [5,6]. However, we faced the fact that acute pain after LC is most intense on the day of surgery, it is complex in nature and consists of a collection of three different and clinically separate components: incisional pain (somatic pain), visceral pain (deep intraabdominal pain), and shoulder pain (presumably referred visceral pain) [4]. Several experiments were conducted to treat post-LC pain, including the use of multiple analgesic modalities, preemptive nonsteroidal anti-inflammatory medications or opioid use, and local

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anesthetic infiltration of the port sites. Several studies in recent years have reported that IP administration of local anesthetics at the end of LC provides effective postoperative analgesia. Some of them used IP administration of non-diluted bupivacaine (20 ml of 0.5%) as Toleska et al. 2018 [6] and Vijayaraghavalu et al. 2021 [7], but the duration of post-operative analgesia was not sufficiently long. While, others used diluted bupivacaine 0.5% (20 ml was diluted in 500 ml normal saline) as Manan et al. 2020 [4] and Jain et al. 2018 [5] who reported longer duration of postoperative analgesia. Providing adequate analgesic medication following LC has proven to be a clinical challenge, so we now have to offer a safe pain-free maneuver because we are dealing with a very popular procedure. Our study aims to compare between the postoperative analgesic effect of IP instillation of diluted versus non-diluted bupivacaine after LC.

2. Patients and methods

2.1. Study design

This prospective randomized single blinded study was conducted in Sohag University Hospital on 50 patients undergoing elective LC, after taking approval from medical ethics (institutional review board) of Sohag Faculty of Medicine under IRB Registration number: Soh-Med-23–07-1PD and obtaining written informed consent from every patient.

2.2 Inclusion criteria

- Aged from 18 to 60 years of both genders.
- American Society of Anesthesiology as ASA I and II.
- All participants were scheduled for elective LC under general anesthesia.

2.3. Exclusion criteria

- Patient refusal.
- Individuals with a history of drug allergies (bupivacaine, paracetamol, and tramadol).
- Body Mass Index (BMI) > 40 kg/m^2.
- Patients on chronic pain medications.
- Acute cholecystitis.
- Coagulation and bleeding disorders.
- Prior abdominal surgery.
- Pregnant or lactating woman.
- Patients who had their operation converted to an open cholecystectomy or who had problems that could have increased postoperative discomfort, such as biliary leakage due to gall bladder puncture or extensive dissection due to adhesions or choledocholithiasis.

3. Randomization

- The patients were randomly divided by computer-generated random number technique into three groups, each of which contained 25 patients by using sequentially numbered envelopes.
- Group BN (BNG) received IP instillation of 20 ml bupivacaine 0.5%.
- Group BD (BDG) received IP instillation of 20 ml of bupivacaine 0.5% diluted in 480 ml normal saline (total 500 ml).

Sample size calculation was conducted based on the results of a study done by Vijayaraghavalu and Bharthi Sekar [7] who conducted 60 participants with 30 patients in each group; they gave 30 ml normal saline in group A and gave 30 ml of bupivacaine 0.5% in group B. In that study, the mean VAS score in group B was 1.56 at 0 h, 1.99 at 2 h, 2.11 at 4 h, 2.45 at 6 h, 3.36 at 12 h, and 3.53 at 24 h. The mean VAS score in group A was 3.46 at 0 h, 3.83 at 2 h, 3.90 at 4 h, 4.22 at 6 h, 4.32 at 12 h, and 4.38 at 24 h. A sample size of a minimum of 22 patients in each group was necessary to provide $\alpha = 0.05$ and power of study 80%. We enrolled 25 patients in each group to compensate for patients excluded during the study. All patients received a thorough explanation of the visual analog scale (VAS). The VAS is a straight, vertical 10 cm line, with the lowest point (0 cm) designating no pain and the top (10 cm) designating the most excruciating agony conceivable [8]. Standard monitoring was started as soon as the patient entered the operation room, including noninvasive blood pressure, electrocardiogram (ECG), and pulse oximetry (SpO_2). An intravenous 18 G cannula was then placed, and 10 ml/kg of Ringer's solution was administered. All patients were pre-oxygenated with 100% O_2 for 3 min and premedicated with midazolam 0.05 mg/kg before starting anesthesia. Fentanyl 2 mcg/kg and propofol 1% 2.0–2.5 mg/kg were used to induce anesthesia, and rocuronium 0.5 mg/kg was then administered to help with tracheal intubation using an appropriately sized cuffed endotracheal tube. Inhalational isoflurane 1.5–2% in 40% oxygen was used to maintain anesthesia in order to maintain mean arterial pressure (MAP) and heart rate (HR) around baseline levels. Respiratory rate and tidal volume of 6–8 ml/kg were used to control ventilation. End-tidal CO_2 was kept between 35 and 40 mmHg by adjusting the ventilation parameters. Throughout the procedure, the intra-abdominal pressure was maintained between 12 and 15 mmHg by insufflating CO_2 to induce pneumoperitoneum. Once the gall bladder has been extracted, the peritoneal cavity was cleaned, hemostasis was achieved, irrigation fluid was suctioned, and before wound closure; patients of DBG received 480 ml normal saline +20 ml of 0.5% bupivacaine (total 500 ml), while patients of NBG received intraperitoneal

instillation of bupivacaine 0.5% 20 ml. Each patient was then placed in the Trendelenburg position for 5 min while the surgeon administered the study solutions intraperitoneally, randomly and directly under vision into the right hepato-diaphragmatic space, on the gall bladder bed, close to and above the hepatoduodenal ligament. The instillation was completed utilizing an intravenous set in DBG or 20 ml syringe in NBG connected to the uppermost trocar (epigastric) used during surgery. No intraperitoneal drain and no suction of the instilled fluid. The trocar sites were not infiltrated with local anesthetic. Neostigmine 0.05 mg/kg and atropine 0.01 mg/kg were used to reverse the neuromuscular blockade after the surgery and inhalational anesthesia was discontinued. After being extubated, patients were taken to the PACU (the 1st reading in PACU considered the zero reading). Patients did not receive any prophylactic anti-emetic drugs, to accurately measure post LC negative effects, but we allowed administration of anti-emetic (ondansetron 0.1 mg/kg) to any patient who developed nausea or vomiting. The only analgesic the patients got during surgery was paracetamol 1000 mg.

Monitoring of HR, MAP, and SpO_2 was done in the PACU. For the first 30 min and collected every 10 min following recovery. VAS score from 0 (no pain) to 10 (most severe pain) was used to gauge the intensity of the pain [8]. Patients completed pain assessments at the following time intervals: immediately following admission to PACU (declared as 0 h), then at 1, 2, 4, 6, 8, 10, 12, and 24 h following surgery. Rescue analgesia was administered using tramadol 1 mg/kg i.v. after recovery (considered as 0 h) and along 24 h postoperatively for patients with VAS ≥ 4. It was recorded when the first analgesic request occurred, how much tramadol was used overall in the first 24 h following surgery and the number of patients who needed rescue analgesia. We reported the negative effects after LC including nausea, vomiting, shoulder pain, or side effects due to analgesic drugs such as hypotension (>20% reduction in MAP from baseline), bradycardia (HR < 60 bpm), respiratory depression (SpO2 < 90% on room air &/or respiratory rate < 10 breaths/min).

Our primary outcome was the postoperative pain relief measured by Visual Analogue Scale (VAS), whereas the time to first analgesic request, the total amount of analgesic consumed in a 24-h period, relieve of negative effects after LC as nausea, vomiting, and shoulder pain, absence of side effects due to bupivacaine as hypotension, bradycardia, or respiratory depression and hemodynamic variations were the secondary outcomes.

3.1. Statistics

Data were analyzed using STATA version 17.0 (Stata Statistical Software: Release 17.0 College Station, TX: StataCorp LP.). The Kolmogorov–Smimov test is used to verify the normal distribution of continuous variables. Quantitative data was represented as mean, standard deviation, median, and range. Normally distributed data was analyzed using student test. For non-normally distributed data Mann Whitney test was used. Qualitative data were presented as number and percentage and analyzed using chi or Fisher's exact test, as appropriate. Graphs were produced by using Excel program. *P* value was considered significant if it was less than 0.05.

4. Results

All patients of both groups were comparable in terms of demographic data such as age, weight, height, sex, the duration of surgery and duration of anesthesia; *P* value ˃0.05 (Table 1). No patient was excluded from the study as described in the flow chart (Figure 1). Throughout the whole trial period up to 24 h postoperatively, the VAS values of DBG were significantly lower than NBG, at base line (immediately postoperative), at 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, and at 24 h postoperatively, the *p* value was 0.0001, 0.0001, 0.0005, 0.003, 0.001, 0.0001, 0.0001, 0.0001, 0.0001, 0.001, respectively. (Table 2)

The time to the first analgesic request was significantly longer in DBG (20.16 ± 3.52 h) than that in NBG (6.19 ± 2.93 h) as *p* value = 0.0001 along 24 h indicating better and longer duration of postoperative analgesia in DBG. We found that only three patients received rescue analgesia in DBG; while, in NBG 16 patients asked for rescue analgesia throughout the postoperative 24 h.

Total analgesic dose (tramadol) in mg throughout 24 h were significantly lower in DBG (7.2 ± 19.9 mg) than NBG (63 ± 31.19 mg) with *p* value = 0.0001 (Table 3).

In relation to negative effects after LC; no significant difference between DBG and NBG in the incidence of nausea, vomiting, and shoulder pain (*P* value ˃ 0.05). Furthermore, none of the study participants in both groups experienced side effects due to local anesthetic instillation such as hypotension, bradycardia, or respiratory depression (Table 4).

When we compared the hemodynamic alterations in HR and MAP during 0, 10, 20, and 30 min post recovery; DBG and NBG had normal, comparable values, with no significant difference (*P* value ˃ 0.05). In relation to SpO_2 there was no significant decrease in both groups (no respiratory depression), however there was a significant increase in SpO_2 in DBG in relation to NBG immediately after recovery (0 time) and at 10 min later, without significant difference along the rest of postoperative period of SpO_2 measurement (Figures 2, 3 , and 4).

Table 1. Demographic characteristics of the patients in DBG and NBG.

Variable	DBG $N = 25$	NBG $N = 25$	p-value
Age (years)			
Mean ± SD	48.77 ± 10.50	47.42 ± 13.18	0.73
Median (range)	52 (32:61)	56.5 (25.5:60)	
Gender			
Female	15 (60.00%)	16 (64.00%)	0.77
Male	10 (40.00%)	9 (36.00%)	
Height (cm)			
Mean ± SD	160.04 ± 4.42	158.36 ± 5.94	0.81
Median (range)	160 (151:168)	158 (149:169)	
Weight (kg)			
Mean ± SD	68.07 ± 8.04	68.07 ± 8.04	1.00
Median (range)	65.5 (55:83)	65.5 (55:83)	
ASA class			
I	19 (76.00%)	20 (80.00%)	0.73
II	6 (24.00%)	5 (20.00%)	
Duration of surgery (min)			
Mean ± SD	62.48 ± 12.23	66.84 ± 15.76	0.32
Median (range)	64 (42:82)	65 (45:90)	
Duration of anesthesia (min)			
Mean ± SD(min)	84.4 ± 15.72	80.24 ± 12.13	0.37
Median (range)	82 (63:110)	81 (59:100)	

Note: p-value compared both groups. SD=Standard deviation. F/M: Female/Male. min= minutes.

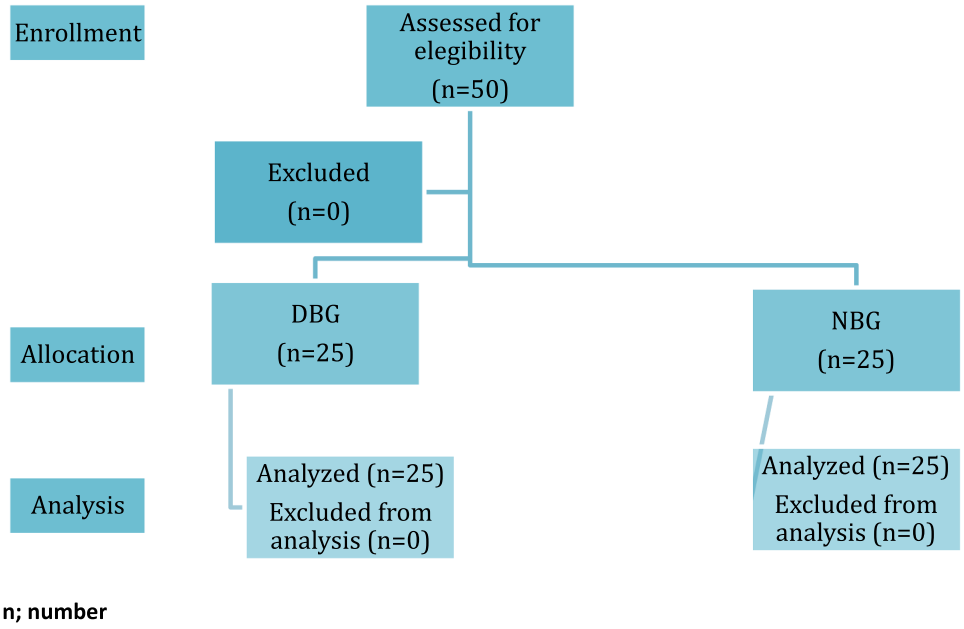

Figure 1. Flow diagram showing participants enrollment, allocation and analysis. Note: n; number. Authors own figure

5. Discussion

The first LC surgery was performed by Dr. Med Erich Mühe nearly four decades ago. From that point on, the procedure underwent continuous development until it was widely accepted as the best way to treat symptomatic cholelithiasis [9,10].

Laparoscopic approach for different surgeries has many advantages when compared to open surgeries including less post-operative pain, less analgesic requirements, early mobilization, and less post-operative hospital stay, Improved postoperative respiratory function, quick recovery of gastrointestinal function, shorter recovery time, less surgical wound infection, and better outward look [11].

Despite all the benefits of LC, postoperative pain after LC is still an issue that needs to be resolved. Many surgeons employ intraperitoneal IP local anesthetic delivery to effectively relieve pain, while reducing the side effects of systemic analgesics [5].

In this study, all patients of both groups were similar in terms of demographic data as follows: age, weight, height, sex, the duration of surgery and duration of anesthesia

Our research found that IP instillation of diluted bupivacaine 100 mg in 500 ml normal saline (DBG) produced effective postoperative pain control than

Table 2. VAS scores in DBG and NBG.

Variable	(DBG) $N = 25$	(NBN) $N = 25$	p-value
At baseline			
Mean ± SD	0.88 ± 0.78	2.08 ± 0.76	0.0001*
Median (range)	1 (0:2)	2 (1:3)	
At 1 hour			
Mean ± SD	2.16 ± 0.85	2.16 ± 0.75	0.0005*
Median (range)	1 (0:2)	2 (1:3)	
At 2 hours			
Mean ± SD	1.36 ± 0.99	2.24 ± 0.72	0.003*
Median (range)	1 (0:3)	2 (1:3)	
At 4 hours			
Mean ± SD	1.68 ± 0.85	2.32 ± 063	0.001*
Median (range)	2 (0:3)	2 (1:3)	
At 6 hours			
Mean ± SD	1.84 ± 0.75	3.76 ± 0.66	0.0001*
Median (range)	2 (1:3)	4 (3:5)	
At 8 hours			
Mean ± SD	2.08 ± 0.64	4.32 ± 0.69	0.0001*
Median (range)	2 (1:3)	4 (3:5)	
At 10 hours			
Mean ± SD	1.64 ± 0.86	4.52 ± 0.87	0.0001*
Median (range)	1 (0:3)	5 (3:6)	
At 12 hours			
Mean ± SD	1.72 ± 0.74	2.84 ± 0.75	0.0001*
Median (range)	2 (1:3)	3 (2:4)	
At 24 hours			
Mean ± SD	1.48 ± 1.12	2.32 ± 0.9	0.003*
Median (range)	1 (0:4)	2 (0:4)	

Note: p-value compared both groups. SD=standard deviation, * = significant.

Table 3. Time to 1st analgesic request, number of patients requiring analgesia and total tramadol dose (mg) in DBG and NBG.

	DBG	NBG	p-value
Time of 1st analgesic request (h)	20.16 ± 3.52	6.19 ± 2.93	0.0001*
No. of patients requiring analgesia in 24 hrs	3	22	
Total tramadol dose(mg)(mean ± SD)	7.2 ± 19.9	63 ± 31.19	0.0001*

Note: SD= standard deviation. h=hour. P-value that compare both groups, mg; milligram, * = significant.

Table 4. Postoperative negative effects due to LC pain and side effects of bupivacaine in DBG and NBG.

	DBG (n)	GBN (n)	p-value
Nausea	2	3	0.55
Vomiting	1	2	0.55
Pain at shoulder area	0	2	0.15
Hypotension, Bradycardia, Respiratory depression	0	0	

Note: n = number of patients. P-value: that compare both groups.

non-diluted bupivacaine 100 mg 0.5% in 20 ml (NBG) which proved by lower VAS values, a longer time to the first analgesic request, a lower overall use of rescue analgesics, and less total number of patients requiring rescue analgesia in DBG than NBG along the first post-operative 24 h.

This can be attributed to the large volumes that are able to effectively cover a large surface area of sub-hepatic space, the surrounding peritoneum, and even the incisions of port inlets. Also, its continuous existence after surgery (no aspiration or drainage) increased the contact period, producing longer post-operative analgesia time. Since no other study has compared the analgesic effects of IP instillations of diluted and non-diluted bupivacaine following LC, we contrasted our study to others that looked at each studied group independently (unique study up to this time).

Many studies investigated the analgesic effect of IP instillation of diluted bupivacaine, for example, ***Jain et al.*** [5] who compared between IP administration of diluted bupivacaine (20 ml 0.5% bupivacaine in 480 ml normal saline) Vs normal saline (500 ml), 30 patients for each group, and they concluded that intraperitoneal bupivacaine of big volume with small concentrations was effective in postoperative analgesia after LC, as significantly lowers numeric pain rating scale (NRS) in agreement with low VAS score in our study, and long time for first analgesic request (19.35 ± 8.64 h), contrasted to (20.16 ± 3.52 h) in our work, total rescue tramadol requirements (23.33 ± 43.01 mg) compared to (7.2 ± 19.9 mg) in ours, total number of patients (only seven patients) required rescue analgesia, and only three in ours. As regard to the amount of rescue analgesia (tramadol) was less in our study, this can be explained by the duration of postoperative analgesia which was 1 h more in our study, so we gave less amount of rescue analgesia, pain assessment in ***Jain*** study

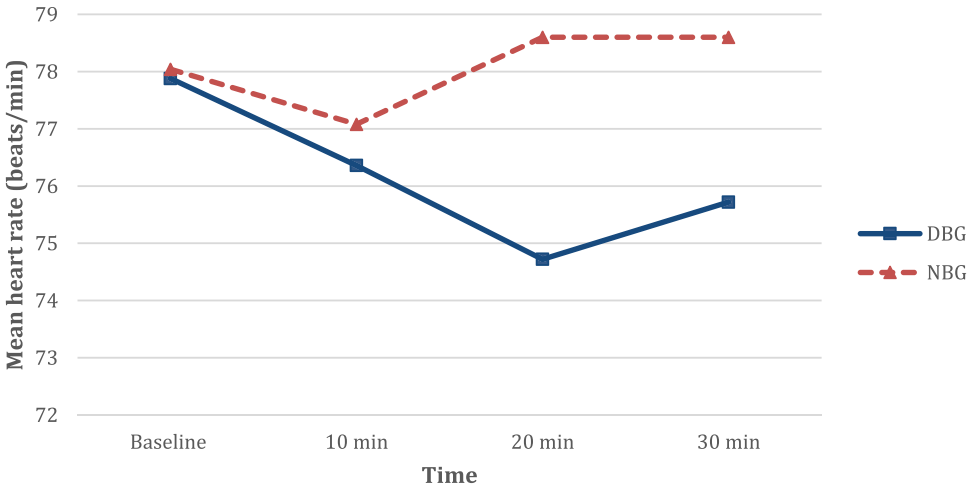

Figure 2. Post recovery heart rate of studied population.

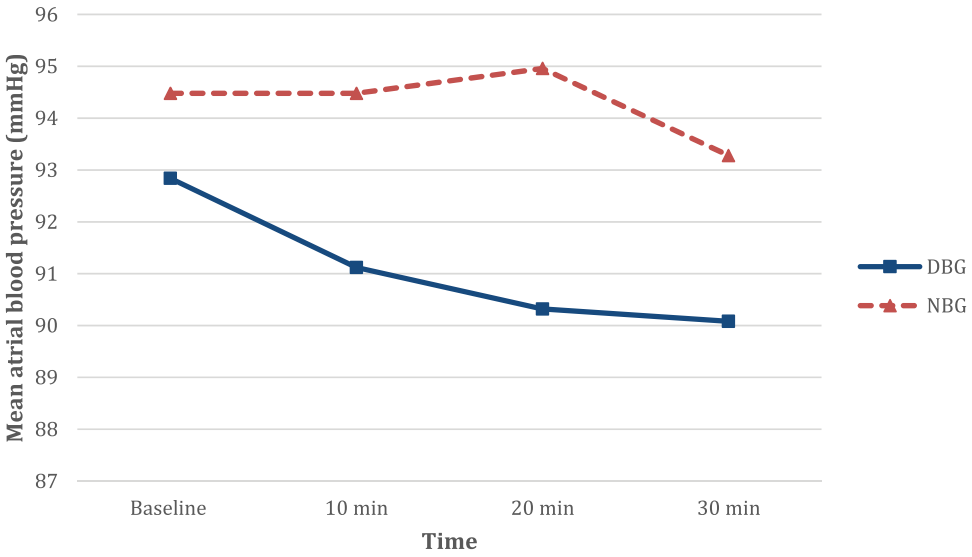

Figure 3. Post recovery mean atrial blood pressure of studied population.

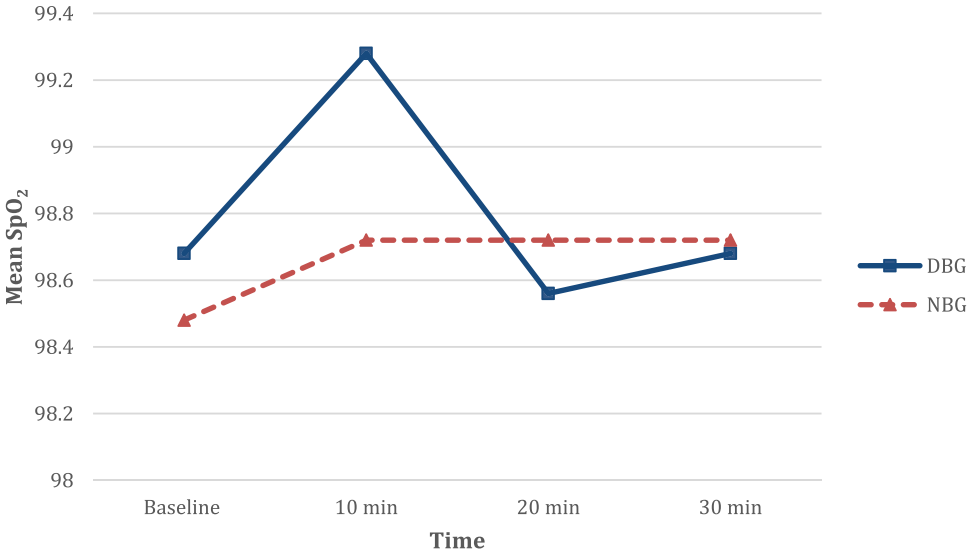

Figure 4. Post recovery SPO2 of studied population.

done by numeric pain rating scale (NRS) in contrast to ours (by VAS) also, they removed the instilled bupivacaine fluid and we did not remove it.

Another study in agree with our results in DBG patients, done by ***Manan et al.*** [4] who compared between irrigation of 500 ml normal saline in one group versus 20 ml 0.5% bupivacaine (100 mg) added to 480 ml normal saline in other group, 55 patients in each group and reported that bupivacaine when diluted in big volume and instilled intraperitoneally in LC gives prolonged analgesia, as the mean duration of analgesia time in their diluted bupivacaine group was 16.53 ± 2.65 h which was shorter than our study and the amount of rescue analgesic of tramadol was 31.00 ± 14.98 mg which was more than ours. These differences can be attributed to pain assessment in ***Manan*** study done by numeric pain rating scale (NRS) in contrast to ours by VAS, duration of postoperative analgesia in our study was approximately 4 h more than Manan study so we gave less amount of rescue analgesia, and also, we did not remove any of the analgesic solution, while Manan did.

Furthermore, many studies investigated the analgesic effect of IP instillation of low volume (20 ml), high concentration of bupivacaine (100 mg 0.5%) in LC. In a study done by **Vijayaraghavalu et al**. [7] where they compared IP administration of 30 ml bupivacaine 0.5% versus 30 ml normal saline for 30 patients in each group, they reported that the VAS score was low, in their non-diluted bupivacaine group, only up to 6 h postoperatively. The mean time taken for the first analgesic request was 182.83 min in the bupivacaine group. This finding was similar to the results reported by Devalkar and Salgaonkar (162.22 ± 124.16 min) [12] and by Suma and Vikranth (3.2 h) [13]. However, the latter used a 20 ml of bupivacaine 0.25%. These results agree with our study.

Another study done by ***Toleska et al.*** [6] where 50 patients scheduled for LC were divided into two groups; one group received IP instillation of 0.5% bupivacaine (20 ml) and the other group received nothing. They found that there were statistically significantly lower VAS scores in the bupivacaine group at all postoperative time points (1 hr, 4 hr, 8 hr, 12 hr, and 24 hr). It is comparable with our NBG for up to 8 h as our VAS scores were low and after that our VAS scores were higher. This can be explained by using high intraabdominal pressure up to 15 mmHg in our study, while in Toleska study they maintained it at 12 mmHg, which might lead to more postoperative pain.

Also, another study of concentrated, low volume bupivacaine, done by ***Banoria et al.*** [14] They enrolled 64 patients undergoing LC and divided them into two groups (A and B). In group (A) IP administration of the under surface of the diaphragmatic and the bed of the removed gallbladder fossa was performed with 20 ml of 0.5% bupivacaine, while in group (B) nothing was given. They discovered that Post-op pain relief in first 8 h was better in the bupivacaine group with decreased postoperative VAS scores and postoperative analgesic requirements, in agreement with our NBG results.

In contrast to our findings, several researches [11–14] did not report that the IP instillation of bupivacaine at the conclusion of LC surgery provided effective postoperative pain relief. **Joris et al**. [15] reported that the instillation of 80 ml 0.125% bupivacaine intraperitoneally was not effective for managing pain after LC, which can be explained by the use of low bupivacaine dose and concentration. **Scheinin B et al**. [16] study concluded that post-surgical IP instillation of 150 mg bupivacaine in 100 ml of saline had no effect on pain after LC. In ***Zmora et al.*** trial [17] where 60 patients underwent elective LC were prospectively divided into two groups. Following the removal of the gallbladder, group A received 100 mg of bupivacaine in 50 cc of saline, injected into the gallbladder bed and right subphrenic space. Group B received normal saline. They did not note any benefits of IP bupivacaine instillation for postoperative analgesia following LC. This may be attributed to the smaller number of patients in their study, where nine patients were excluded owing to conversion to an open cholecystectomy and having a drain left in the peritoneal cavity. Additionally, their pain assessment was done at different time intervals (at 1, 2, 4, and 14 h after surgery). Also, ***Jiranantarat et al.*** [18] reported that IP instillation of bupivacaine does not show any advantage for postoperative analgesia after LC. Regarding postoperative negative effects after LC, in our study, there was a significant decrease in the number of patients who experienced nausea, vomiting, and shoulder pain in DBG and NBG, with no side effects due to bupivacaine use such as bradycardia, hypotension, or respiratory depression. ***Jain et al.*** [5], reported no nausea or vomiting, while in our (DBG) one patient showed nausea and two patients in NBG showed vomiting, and this difference may be due to the administration of ondansetron 0.1 mg/kg preoperatively to all patients in Jain's study. As for the side effects of bupivacaine, there were no significant side effects in Jain's study, in agreement with our research. ***Manan et al.*** [4] reported no nausea or vomiting contrasted to two patients who showed nausea and one with vomiting in our study, but they did not mention if they used prophylactic antiemetic or not. In **Vijayaraghavalu's study** [7] nausea occurred in one patient, vomiting in two patients which was quite similar (nausea three patients and vomiting two patients) to our NBG. Meanwhile, shoulder pain was found in seven patients in their bupivacaine group, contrasted to two patients in our NBG. Also, no side effects mentioned in their study due to bupivacaine, which agree with ours.

A study done by **Javed et al**. [19] who studied 110 patients scheduled for LC and divided the patients into

two groups (A and B). Group A were instilled IP 20 ml of normal saline and Group B were instilled IP 20 ml of 0.25% bupivacaine after completion of the procedure, and they reported that there was a decrease in the incidence of nausea, vomiting, and shoulder pain, the same as our results.

When we compared the hemodynamic alterations in HR and MAP during post-recovery period, DBG and NBG had normal, comparable values, with no significant difference but in relation to SpO_2 there was no significant decrease in both groups (no respiratory depression), however there was significant increase in SpO_2 in DBG in relation to NBG immediately after recovery, which indicate more effective pain relieve at early postoperative time, without significant difference along the rest of postoperative period of SpO_2 measurements. In agreement with our results, ***Ali et al.*** [1], ***Jain et al.*** [5] and **Vijayaraghavalu** [7], studies reported no significant hemodynamic changes in their bupivacaine group.

6. Conclusion

Intraperitoneal instillation of diluted bupivacaine at the end of laparoscopic cholecystectomy decreases postoperative pain, delays request for rescue analgesia, and reduces the amount of analgesics in the first 24 h postoperatively more than non-diluted bupivacaine, with comparable results in relieving negative effects after LC, side effects due to analgesic drugs and comparable hemodynamic parameters.

7. Limitations

We did not investigate or record pain during coughing or movement. Also, our study's weakness stems from the limited sample size and low statistical power. More conclusive data will be established with a larger sample size.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

[1] Ali WA, Ali NS, Sewefy AM, et al. Comparative study between intraperitoneal bupivacaine and bupivacaine-nalbuphine for postoperative pain relief after laparoscopic cholecystectomy. Res Opin Anesth Intensive Care. 2020;7(1):57–64. doi: 10.4103/roaic.roaic_101_18

[2] Pisano M, Allievi N, Gurusamy K, et al. World Society of Emergency surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis. World J Emerg Surg. 2020;2020(1):61. doi: 10.1186/s13017-020-00336-x

[3] Ravishankar N, Vasudevaiah T, Shivkumar S. Irrigation with bupivacaine at surgical bed for postoperative pain relief after laparoscopic cholecystectomy. Int Surg J. 2018;5(4):1538–42. doi: 10.18203/2349-2902.isj20181144

[4] Manan A, Khan AA, Ahmad I, et al. Intraperitoneal bupivacaine as post-laparoscopic cholecystectomy analgesia. J Coll Physicians Surg Pak. 2020;30(1):9–12. doi: 10.29271/jcpsp.2020.01.09

[5] Jain S, Nazir N, Singh S, et al. A prospective randomized controlled study for evaluation of high-volume low-concentration intraperitoneal bupivacaine for post-laparoscopic cholecystectomy analgesia. Indian J Anaesth. 2018;62(2):109–14. doi: 10.4103/ija.IJA_87_17

[6] Toleska M, Kartalov A, Kuzmanovska B, et al. Efficacy of intra-peritoneal bupivacaine on pain relief after laparoscopic cholecystectomy. Pril Makedon Akad Nauk Umet Odd Med Nauki. 2018;39(1):123–9. doi: 10.2478/prilozi-2018-0032

[7] Vijayaraghavalu S, Bharthi Sekar E. A Comparative study on the postoperative analgesic effects of the intraperitoneal instillation of bupivacaine versus normal saline following laparoscopic cholecystectomy. Cureus. 2021 Mar 27;13(3):e14151. doi: 10.7759/cureus.14151

[8] Raheem MA, Abbas Badawy F, Hitham ME. Comparative study of analgesic effect of epidural ketamine vs. epidural tramadol in patients undergoing mastectomy under thoracic epidural anesthesia. Egypt J Anaesth. 2022;38(1):672–679. doi: 10.1080/11101849.2022.2143182

[9] WJr R. The first laparoscopic cholecystectomy. JSLS. 2001 Jan-Mar;5(1):89–94. PMID:11304004; PMCID: PMC3015420.

[10] Litynski GS. Highlights in the history of laparoscopy. Frankfurt, Germany: Barbara BernetVerlag; 1996. pp. 165–168.

[11] Lao LS, Torillo ML, Hao PPR. Efficacy of intraperitoneal bupivacaine on postoperative analgesia in laparoscopic cholecystectomy. A meta-analysis. J Am Coll Surg. 2017;225(4):e85. doi: 10.1016/j.jamcollsurg.2017.07.754

[12] Devalkar PS, Salgaonkar SV. Intraperitoneal instillation of 0.25% bupivacaine for laparoscopic cholecystectomy: effect on postoperative pain. IJCMAAS. 2016;12:91–5.

[13] Suma S, Vikranth SN, Nikhil M. Intra-peritoneal bupivacaine instillation for post-operative pain relief after laparoscopic cholecystectomy: a prospective study. Int J Contemp Surg. 2019;7(2):108–114. doi: 10.5958/2321-1024.2019.00033.3

[14] Banoria NK, Prakash S, Sharma OK. Effect of local anesthetic instillation intraperitoneally on post-op pain relief after laparoscopic cholecystectomy. Indian J Clin Anat Physiol. 2016 Jul;3(3):322–325. doi: 10.5958/2394-2126.2016.00073.6

[15] Joris J, Tlury E, Paris P, et al. Pain after laparoscopic cholecystectomy: characteristic and effect of intraperitoneal bupivacaine. Anesth Analg. 1995;81(2):379–384. doi: 10.1213/00000539-199508000-00029

[16] Scheinin B, Kellkumpu I, Lindgren L, et al. Effects of intraperitoneal bupivacaine on pain after laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 1995;39(2):195–198. doi: 10.1111/j.1399-6576.1995.tb04042.x

[17] Zmora O, Stolik-Dollberg O, Bar-Zakai B, et al. Intraperitoneal bupivacaine does not attenuate pain

following laparoscopic cholecystectomy. JSLS. 2000;4 (4):301–304.

[18] Jiranantarat V, Rushatamukayanunt W, Lert-Akyamanee N, et al. Analgesic effect of intraperitoneal instillation of bupivacaine for postoperative laparoscopic cholecystectomy. J Med Assoc Thai. 2002;85:897–903.

[19] Javed SA, Muham HK. Pre-emptive analgesia in laparoscopic cholecystectomy by intraperitoneal instillation of bupivacain. J Fatima Jinnah Med Uni. 2016;10:56–9.