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Effect of Different Concentrations of Intraperitoneal Bupivacaine on Postoperative Outcome in Morbidly Obese Patients Undergoing Laparoscopic Bariatric Surgery

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Abstract: Introduction: Regional analgesic techniques with infiltration of local anesthetic represent a cornerstone in modern postoperative pain management strategies after laparoscopic surgery. If used in a right concentration, it could help in attenuation of postoperative pain with better pulmonary performance and less morbidity. Aim: to compare the effect of different concentrations of intraperitoneal bupivacaine to obtain proper pain relief after laparoscopic bariatric surgery and evaluating its effect on pulmonary functions. Patients and methods: One hundred and twenty morbidly obese patients were included in this study. Patients were divided into three group. Group (A) patients received 50 ml bupivacaine 0.25% into the coelomic cavity. Group (B) patients receive 50 ml bupivacaine 0.125% into the coelomic cavity. Group (C) control group (n=36): patients receive 50 ml of normal saline into the coelomic cavity. VAS score and pulmonary function study were examined before and at regular intervals after surgery. Total analgesic requirements and time to first analgesic rescue was recorded. Results: VAS in group (A) was significantly lower than group (C) 2 hours after surgery and lower in group (A) compared with group (B&C) at 4 and 6 hours postoperative. Postoperative morphine consumption was lower in group (A) during the first 24 hours when compared to group (B & C) respectively. Both FVC and FEV1 were higher in group (A) compared to group (B&C) at 6hours postoperative. Conclusion: intraperitoneal injection of bupivacaine 0.25% is an efficient method of decreasing the postoperative pain with better preservation of pulmonary functions in morbidly obese patients undergoing laparoscopic bariatric surgery.

Keywords: Analgesia, Bariatric Surgery, Pain Score, Pulmonary Functions, Recruitment Maneuvers

1. Introduction

Laparoscopic surgical approach has widely replaced conventional surgical techniques over the last two decades especially in bariatric surgical field. Their prevalence may be attributed to their ability to improve postoperative pain, nausea and vomiting, recovery time and respiratory function in comparison to old open techniques which help in quicker recovery and discharge from the hospital [1].

In order to obtain adequate postoperative pain management after laparoscopic surgery, a multimodal combination of non-steroidal anti-inflammatory drugs, opioids, and local anesthetic infiltration has been employed [2].

Local anesthetic medications can be administered inside the peritoneal cavity through laparoscopic ports either immediately after creation of the surgical incision or before

closure. It can also be infiltrated into the surgical bed after organ removal, below the diaphragm or over visceral peritoneum. This may help in attenuation of shoulder pain which frequently observed after laparoscopic surgery [3]. Different local anesthetics have been injected inside the peritoneal cavity in different doses to obtain proper post laparoscopic analgesia [4]. Up till now, there is a debate between researchers about the optimal effective and safe concentration of these local anesthetics used in intraperitoneal infiltration. Up to our best knowledge, there is no previous study has investigated the safety and efficacy of different concentrations of bupivacaine injected intraperitoneally for post laparoscopic analgesia and their implication on respiratory performance.

2. Aim of the Work

The primary aim of this study was to compare the analgesic effect of different concentrations of intraperitoneal bupivacaine for pain relief after laparoscopic bariatric surgery. The secondary aim was to evaluate their effect on pulmonary ventilation functions. In order to investigate these outcomes, total analgesic requirement, visual analogue score, the time to first analgesic request and pulmonary functions test were used.

3. Patients and Methods

Patients: This double-blind randomized controlled study was conducted in Mansoura University Hospitals, between September 2018 and March 2020 after obtaining the Institutional Research Board Approval Number R. 19.01.399, Mansoura Faculty of Medicine. Registered with UMIN ID: UMIN000038595. A written informed consent was obtained from every patient before inclusion in the study.

Inclusion criteria: One hundred and twenty morbidly obese patients with body mass index (BMI) $\geq$35 kg.m^2 and aged between 18–60 years with the American Society of Anesthesiologists physical Class I–II who were planned for laparoscopic sleeve gastrectomy under general anesthesia were included in this study.

Exclusion criteria: Patients with a history of significant cardiac, hepatic, renal or Psychiatric diseases, Patient refusal, neuromuscular diseases (as myopathies, myasthenia gravies), known intolerance to the study drugs or patients converted to open gastric bypass or laparotomy were excluded.

Methods: Preoperative pulmonary function study was done for every patient and the forced vital capacity (FVC) and forced expiratory volume in first second (FEV1) were recorded. All patients were familiarized with 100-mm visual analogue scale score (VAS) identifying zero as no pain and 100 as the worst imaginable pain. On patient arrival to the anesthetic room, standard monitoring including 5 leads electrocardiography, non-invasive blood pressure and pulse oximetry were attached to the patient. Peripheral intra-venous cannula (18 G) was be inserted and Lactated Ringer's solution infusion was started.

All medications' doses used in this study protocol were calculated based on the lean body weight (ideal body weight (IBW) +0.4× [actual body weight – IBW]) as described by Han et al [5].

All patients were pre medicated with midazolam 0.05mg.kg^{-1} IV. In operative room, all patients were pre-oxygenation with 100% oxygen for three minutes at rate of 6 L.min^{-1}, general anesthesia was induced using IV propofol at dose of 2-3 mg.kg^{-1}, fentanyl 1 μ.kg^{-1} and rocuronium 1 mg.kg^{-1} to facilitate endotracheal intubation. Patient were mechanically ventilated using a volume control mode with tidal volume 6 ml.kg^{-1} of ideal body weight (IBW), end expiratory pressure of 5 mmHg and respiratory rate was adjusted to maintain end tidal CO_2 around 35 mmHg. Anesthesia was maintained using sevoflurane (MAC 1-1.5), and 50% oxygen in air mixture with top up doses of rocuronium. All operations were done by the same surgeons (consultant level).

During pneumoperitoneum creation, intra‐abdominal pressure was maintained between 12–14 mmHg. Patient position was altered from supine to reverse Trendelenburg position with head up to (40°). At the end of surgery, 10 milliliters of bupivacaine 0.25% were injected in laparoscopic ports sites. Intravenous 4 mg of ondansetron and standard analgesic regimen in the form of ketorolac 30 mg and paracetamol 10 ml.kg^{-1} by intravenous infusion (IVI) was administered to all patients then patients were randomly allocated using closed envelop method into one of the three groups.

Group (A) intraperitoneal bupivacaine 0.25% group (A) (n=40): patients received 50 ml bupivacaine 0.25%. Half of the total volume was streamed at the surgical site and the other half was streamed into the coelomic cavity prior to deflation.

Group (B) Intraperitoneal bupivacaine 0.125% group (n=40): patients received 50 ml bupivacaine 0.125% half of the total volume was streamed at the surgical site and the other half was streamed into the coelomic cavity prior to deflation.

Group (C) control group (n=40): patients received 50 ml of normal saline 0.9% was streamed as before.

Study medications were prepared in identical unlabeled syringes a by our pharmacist. All the operating room staff were unaware of the given medications.

Patients were extubated after ensuring adequate neuromuscular blocking reversal with 0.05 mg.kg^{-1} of neostigmine and 0.02 mg.kg^{-1} of intravenous atropine. The duration of the surgery was recorded.

Post-operative analgesia was standardized for all patients as 0.3 mg.kg^{-1} IV Ketorolac every 8 hours and 10 mg.kg^{-1} IV Paracetamol. Pain was assessed by blind investigator using Visual analogue scale (VAS) with 0=no pain and 10=most severe pain. If the patient experienced pain $\geq$3 and $\leq$7, bolus of IV 3 mg morphine was given, if pain score >7, bolus of IV 5 mg morphine was given. Pain was assessed after 30 minutes, if still $\geq$3, additional IV 5 mg morphine was administered. Attention was paid to side effects of opioids.

Total analgesic requirements, time to first analgesic rescue (with VAS ≥ 3 at any time), VAS of pain was recorded at 2, 4, 6, 12 and 24 hours postoperatively. Changes in FVC and FEV1 were investigated at 2, 6, 24 hours postoperatively.

Statistical analysis

Sample size calculation was performed after conducting a pilot study with 10 patients in each group. In that study, the mean postoperative morphine consumption was 10.5, 13, and 14.75 mg in A, B, and C groups, respectively. A sample size of minimum 35 patients in each group was necessary to provide α=0.05 and power of study 80%. We enrolled 40 patients in each group to compensate for patients excluded during the study.

Data was entered using Microsoft Excel, version 2018 and analyzed statistically using Statistical Package for Social Science Program (SPSS 21 for PC, IBM Inc., Armonk, NY). Descriptive statistics were done using means and standard deviations, medians and inter quartile ranges, or numbers and percentages according to the type and distribution of data. Distribution of data was examined using Shapiro-Wilk test. All *p* values less than 0.05 were considered significant. Between groups comparisons were done using Kruskal-Wallis tests with *p* values less than 0.05 were considered significant, and Mann-Whitney tests with *p* values less than 0.016 were considered significant.

4. Results

One hundred and forty‐four patients were assessed for eligibility, 24 patients were excluded preoperatively either due to not meeting inclusion criteria or the patient refused to participate. The rest (8 patients) were excluded from analysis as shown in flow chart in figure 1.

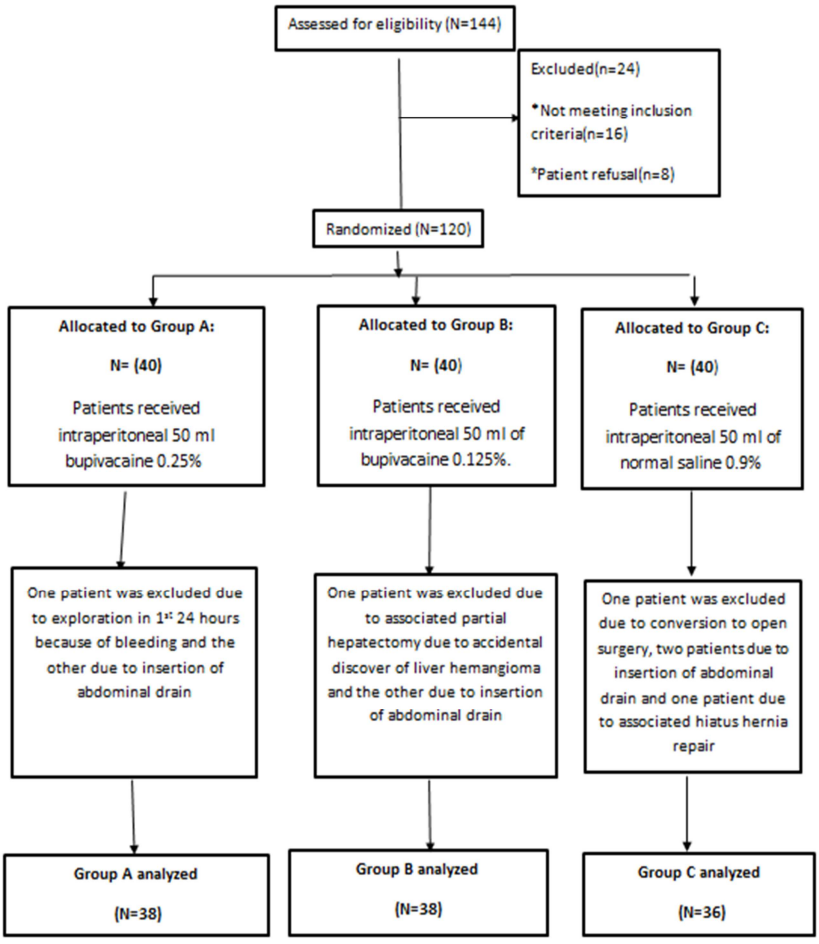

Figure 1. *Study flow diagram.*

There was no significant difference between groups as regard patient characteristics, duration of surgery and baseline FVC and FEV1 (table 1).

Table 1. *Characteristics of participants, duration of surgery and basal FEV1 and FVC of the studied groups. Data are expressed as mean±SD, number and %.*

Variable	Group A (No 38)	Group B (No 38)	Group C (No 36)	*p*	*P1*	*P2*	*P3*
Gender male	15 (39.4%)	14 (36.8%)	7 (19.4%)	0.085	>0.05	>0.05	>0.05
Female	23 (60.5%)	24 (63.4%)	29 (80.6%)				
Age (years)	34.37±7.83	34.34±9.72	33.58±8.07	0.963	1	1	1

Variable	Group A (No 38)	Group B (No 38)	Group C (No 36)	*p*	*P1*	*P2*	*P3*
BMI (kg.m^2)	47.28±5.99	48.21±7.57	49.69±9.20	0.693	1	1	1
Body weight (kg)	131±21	136±23	139±27	0.438	1	0.686	1
Height (m)	1.67±0.09	1.68±0.1	1.67±0.07	0.712	1	1	1
Smoking							
Never	34 (92%)	32 (87%)	31 (86.1%)				
Current	3 (55)	4 (11%)	5 (13.8%)	0.966	>0.05	>0.05	>0.05
Former	1 (3%)	2 (3%)	0 (0%)				
History of medical diseases							
HTN	3 (8%)	7 (19%)	3 (9%)	0.771	>0.05	>0.05	>0.05
DM	2 (5%)	4 (11%)	3 (9%)	0.583	>0.05	>0.05	>0.05
History of abdominal surgeries	6 (16%)	5 (13%)	9 (26%)	0.399	>0.05	>0.05	>0.05
Duration of surgery (minutes)	94±24	89±19	101±27	0.484	>0.05	>0.05	>0.05
Basal FEV1	2.52±0.69	2.55±0.68	2.26±0.56	0.220	1	0.429	0.304
Basal FVC	3.34±0.82	3.28±0.99	2.97±0.81	0.279	1	0.374	0.592

Age and BMI are presented as median (IQR). Weight, height, basal FEV1, and basal FVC are presented as mean±SD. Gender, smoking, medical history, and surgeries are presented as number (%). HTN=Hypertension, DM=Diabetes Mellitus, FEV1=forced expiratory volume in 1st second, FVC=forced vital capacity.

The average amount of postoperative morphine consumption was lower in group (A) (13.63±2.49 mg) during the first 24 hours when compared to group (B & C) (17.79±3.25 and 17.89±3.28) respectively. However, the time to first analgesic request didn't show any differences between all groups (table 2).

Table 2. *Total analgesic consumption in the first postoperative 24 hours and time to first analgesic rescue in the studied groups. Data are presented as mean±SD, median and range.*

variable	Group A (No 38)	Group B (No 38)	Group C (No 36)	*p*	*P1*	*P2*	*P3*
Total morphine consumption (mg)	13.63±2.49	17.79±3.25*	17.89±3.28†	< 0.001	< 0.001	< 0.001	1
Time to first analgesic (minutes)	89.11±18.31	88.18±14.05	80.86±13.32	0.054	1	.065	0.128

* P < 0.05 is considered significant when group B compared to group A.
† P < 0.05 is considered significant when group C compared to group A.
‡ P < 0.05 is considered significant when group B compared to group C.

VAS in group (A) was significantly lower than group (C) 2 hours after surgery. Also, VAS score was lower in group (A) compared with groups (B&C) at 4 and 6 hours postoperative. No differences were found in VAS among the studied groups at 12 and 24 hours after surgery (table 3).

Table 3. *Comparison of Visual Analogue Scale between the studied groups. Data are presented as median and range.*

Time	Group A (No 38)	Group B (No 38)	Group C (No 36)	*p*	*P1*	*P2*	*P3*
2 h after surgery	4 (2 to 5)	5 (3 to 6)	6 (4 to 7)†	0.006	0.314	0.004	0.122
4 h after surgery	5 (2 to 6)	6 (2 to8)*	6 (3 to 8)†	0.009	0.040	0.021	0.603
6 h after surgery	4 (2 to 7)	5 (3 to 7)*	5 (4 to 7)†	0.006	0.008	0.005	1
12 h after surgery	4 (3 to 4)	4 (3 to 4)	4 (3 to 4)	0.685	1	1	1
24 h after surgery	3 (2 to 3)	3 (2 to 4)	4 (3 to 4)	0.295	0.652	0.067	0.358

* P < 0.05 is considered significant when group B compared to group A.
† P < 0.05 is considered significant when group C compared to group A.
‡ P < 0.05 is considered significant when group B compared to group C.

Both FVC and FEV1 were higher in group (A) (80.31±27.18 and 86.82±21.00) when compared to group (B&C) at 6hours postoperative with no differences among all groups at 2 and 24 hours after surgery (table 4).

Table 4. *postoperative FVC and FEV1 percentage from the basal values between the studied groups while excluding effect of consumed analgesics. Data are presented as mean±SD.*

		Group A (No 38)	Group B (No 38)	Group C (No 36)	p	P1	P2	P3
	2 h	75.94±17.17	77.90±25.78	78.38±30.62	0.335	0.660	1	1
FVC	6 h	80.31±27.18	68.46±15.61*	66.28±13.43†	0.014	0.043	0.034	1
	24 h	70.23±11.27	76.03±24.34	76.82±31.68	0.766	0.816	0.824	1
	2 h	73.04±15.93	77.76±24.32	79.02±26.47	0.204	1	0.930	1
FEV1	6 h	81.09±25.43	67.73±24.09*	66.31±23.41†	0.018	0.048	0.043	1
	24 h	72.24±14.32	69.84±16.49	68.73±20.73	0.223	1	1	1

* P < 0.05 is considered significant when group B compared to group A.
† P < 0.05 is considered significant when group C compared to group A.
‡ P < 0.05 is considered significant when group B compared to group C.

5. Discussion

Pain management is crucial for bariatric patients with higher BMI to pass the postoperative period uneventfully. Achieving proper pain management may help with better and effective coughing, chest physiotherapy, lesser nausea and vomiting, early initiation of oral intake and discharge from hospital [6, 7].

Recovery after surgery is affected to a great extent by acute postoperative pain. choosing a multimodal, opioid-free analgesic regime supported with regional nerve blocks or local anesthetic wound infiltration may enable faster return to preoperative functional state [8].

Instillation of local anesthetics in the surgical field has been classically used to decrease postoperative pain, unfortunately, researchers have not properly demonstrated the proper concentration that gives the best analgesic profile, meanwhile doesn't compromise pulmonary functions.

In our current study, total morphine consumption was significantly lower with intraperitoneal bupivacaine 0.25% use when compared with 0.125% concentration (group B) or placebo group ($p< 0.001$). In contrast, the time to first analgesic request didn't show significant difference between the studied three groups.

Alamdari et al [9] in his study, compared the use of intraperitoneal bupivacaine hydrochloride (30 cm3) against control group in patients scheduled for laparoscopic sleeve gastrectomy. He found a significant decrease in pain score and analgesic requirements in patients received intraperitoneal bupivacaine compared to control group.

In another study by safari et al [10] investigating the Effect of 50 ml of Intraperitoneal Bupivacaine 0.2% on Postoperative Pain after Laparoscopic Bariatric Surgeries, they noticed a decrease in Pain level, assessed by visual analogue scale (VAS) at 1, 4, 8 and 24 hours after surgery. Total additive analgesics administered during the first day after surgery was also significantly reduced.

A systematic review and meta-analysis assessing the intraperitoneal anesthetics used in laparoscopic cholecystectomy recommend the use of 20 ml 0.5% (5 mg/ml) bupivacaine for its effective role in reducing postoperative pain and is considered safe [11]. When intraperitoneal bupivacaine compared to postoperative infusion of pethidine after laparoscopic cholecystectomy, bupivacaine was associated with a reduction in pain scores and oral narcotic use [12].

In contrary to our study, a study by Schipper et al compared intraperitoneal bupivacaine injection with placebo in laparoscopic roux en y gastric bypass, they found no significant reduction in pain scores or opioid use in both groups [13].

These findings may be attributed to smaller volume of local anesthetic medications (20 ml) used in that study. Also, they only sprayed the local anesthetic solution on the under surface of diaphragm while other pain sources as dissection at greater omentum and peritoneal insufflation were ignored. Lastly, the type of surgery (roux en-y gastric bypass) is technically different than the surgery done in our study (sleeve gastrectomy)

VAS in group (A) was significantly lower than group (C) 2 hours after surgery. Also, VAS score was lower in group (A) compared with group (B&C) at 4 and 6 hours postoperative. This can be explained by the duration of action of bupivacaine which doesn't extend beyond this duration in these concentrations. At 4 hours, VAS wasn't significant between groups. This might be explained by the higher doses of opioids consumed by groups (B) and (C).

In Cohen et al [14] study, they reviewed the patients' records, who received continuous intraperitoneal infusion of 0.375% bupivacaine. Although postoperative opioid utilization was decreased, the VAS score was not different to control group.

In a different study by Omar et al [15], the intraperitoneal instillation of 40 ml bupivacaine 0.25% was compared with placebo in more than one hundred morbidly obese patients underwent bariatric surgery, they noticed lower VAS records at 2, 4 and 6 h after surgery in bupivacaine group. However, there were no significant differences between both groups at 12 and 24 h postoperatively. This was associated with reduced total analgesic consumption and rescue analgesic requirements.

Pulmonary function while excluded effect of consumed analgesic was studied. Our results revealed a significant reduction in FVC and FEV1 at 6 hours in group (C) than groups (A) and (B) (p 0.012 and 0.015 respectively). There was no significant difference in the percentage of reduction in pulmonary function at 2 and 24 hours.

General anesthesia can affect the respiratory tremendously. It is associated with functional residual capacity (FRC) reduction due to relaxation of the diaphragm and intercostal muscles when FRC approaches closing capacity. This makes small airways and alveoli tend to collapse resulting in Lung atelectasis in about 90% of patients undergoing anesthesia [16].

In the current study, Both FVC and FEV1 were higher in group (A) (80.31±27.18 and 86.82±21.00) when compared to group (B&C) at 6hours postoperative with no differences among all groups at 2 and 24 hours after surgery (table 4). At 2 hours after surgery, the adequate postoperative pain control and proper combined regional or intravenous analgesia given during surgery enable the patients to do effective coughing, early and efficiently pulmonary exercises together with expeditious mobilization. This can explain the absence of any differences regarding FVC and FEVI among the three groups at that time interval [17].

Although pain score was significantly higher in groups (C) than group (A) at 2 hours, this wasn't associated with concomitant difference in pulmonary functions. This could be related to the effect of subdiaphragmatic local anesthetic which keeps the copula up. This action may mask the anticipated preservation of pulmonary function in group (A). Similarly, intraoperative use of lung recruitment maneuvers with open lung approach and application of PEEP limit the

differences between pulmonary functions in the early hours postoperative.

However, at 6 hours following surgery, marked depression in pulmonary functions in group (B) and (C) compared to group (A) at may correlate with significant higher pain scores in these groups at that time. Further studies are required to investigate the relation between intraperitoneal local anesthetics and pulmonary function.

This study has some limitations. First, we depended on nurse controlled analgesia, not patient controlled analgesia. Second, we didn't analyze the rescue analgesic requirements against time domain. However, our primary outcome was total analgesic requirement in 24 hours. We used a portable device for assessing pulmonary functions which is often less accurate than ordinary devices, however we depended on the percentage of decline in FVC and FEV1 from the basal values that was measured by the same device.

6. Conclusion

Intraperitoneal injection of bupivacaine 0.25% is an efficient method of decreasing the postoperative pain with better preservation of pulmonary functions in morbidly obese patients undergoing laparoscopic bariatric surgery.

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