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Intraperitoneal Versus Intravenous Dexmedetomidine for Postoperative Analgesia Following Laparoscopic Sleeve Gastrectomy Surgery: A prospective, Randomized Controlled trial

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ABSTRACT

Background: Postoperative pain control is a major challenge after laparoscopic sleeve gastrectomy. We conducted this study to evaluate the efficacy of dexmedetomidine either intraperitoneal (IP) or intravenous (IV) as an adjuvant to intraperitoneal bupivacaine in patients undergoing sleeve gastrectomy.

Methods: A total of 105 patients were randomized in this prospective, controlled study. All patients received 40 ml bupivacaine 0.25% IP. **Control group** (n = 35): received 50 ml normal saline IV. **IV dexmedetomidine group** (n = 35): received 50 ml normal saline plus dexmedetomidine 1 µg/kg IV. **IP dexmedetomidine group** (n = 35): received IP dexmedetomidine 1 µg/kg plus bupivacaine 0.25%, and 50 ml normal saline IV. Time to first rescue analgesia was the primary outcome. Whereas the total consumption of tramadol and visual analog scale (VAS) were the secondary outcomes.

Results: The first time of rescue analgesia was prolonged in IP dexmedetomidine compared to IV dexmedetomidine and control group ($P < 0.0001$). The total amount of rescue tramadol was lower in IP dexmedetomidine compared to IV dexmedetomidine and control group ($P < 0.0001$). VAS was comparable between the three groups at the recovery room, 2, 4, and 24 h postoperatively, while a statistically significant difference was found at 6, 12, and 18 h postoperatively. Extubation and recovery times were prolonged in IV dexmedetomidine group ($P < 0.0001$, 0.0001; respectively).

Conclusions: IP dexmedetomidine as an adjuvant to IP bupivacaine is as efficacious as IV dexmedetomidine compared to IP bupivacaine alone. However, the IP administration has the longest duration of analgesia and the lowest postoperative analgesic consumption.

Clinical trial registration number: Clinical Trials.gov (NCT04370392).

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Bupivacaine; dexmedetomidine; intraperitoneal; intravenous; gastrectomy; postoperative analgesia

1. Introduction

Morbid obesity incidence has increased worldwide and laparoscopic sleeve gastrectomy has become one of the common surgeries nowadays. [1]

Postoperative pain is usually visceral, parietal, or shoulder tip pain which may be referred due to the intraperitoneal insufflation of CO_2 gas which stretches the abdominal tissues and irritates the diaphragm by the residual amount of gas in the peritoneal cavity. [2] Uncontrolled pain delays early ambulation, which significantly increases the risk of deep vein thrombosis and pulmonary emboli (PE), and decrease patient's ability to take deep breaths leading to increased incidence of pulmonary complications (eg. atelectasis and pneumonia). [3]

Postoperative pain control is a major challenge because of the high prevalence of obstructive sleep apnea among obese patients which limits the use of opioid. Intraperitoneal (IP) local anesthetic administration is a simple and safe technique used to control postoperative pain after laparoscopic surgery.

Hence, we conducted this study to evaluate the antinociceptive effects of dexmedetomidine either intraperitoneal or intravenous as an adjuvant to intraperitoneal bupivacaine in patients undergoing sleeve gastrectomy.

2. Materials and methods

This prospective triple-blinded randomized control study was conducted at Tanta University Hospital between April 2020 and December 2020 after the approval of the institutional ethics committee (approval number: 33,771/4/20), registration in Clinical Trials.gov (NCT04370392), and obtaining a written informed consents from all the participants. A total of 105 obese patients of both sex with BMI > 40 kg/m^2 or > 35 kg/m^2 with comorbidities scheduled for elective laparoscopic sleeve gastrectomy surgery, aged from 20 to 60 years with American Society of Anesthesiologists' (ASA) physical status II or III, were included in this study.

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Patients with known allergy to bupivacaine, prolonged administration of non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics due to chronic pain of any reason, severe renal and hepatic diseases, and patients on anti-hypertensive medication with α_2 adrenergic action were excluded from the study.

Patients were randomly assigned into three groups of 35 patients each at a 1:1:1 allocation ratio using computer-generated random numbers concealed in a sealed opaque envelopes. A blinded nurse, who does not participate in the study or data collection, prepared the group assignments. One anesthetist blinded to group assignment performed the general anesthesia (GA) and responsible for intraperitoneal and intravenous injection of the study medication to all patients at the end of surgery.

A preoperative visit was conducted for history taking; clinical examination and routine preoperative investigations plus pulmonary function test. Patients were trained on how to quantify the intensity of pain using the 10 cm visual analog scale (VAS) (where (0): no pain, (10): maximal imaginable pain).

On arrival to the operating theatre, standard monitoring including a five-lead electrocardiogram (ECG), non-invasive blood pressure (NIBP), and pulse oximetry was applied to all patients. After the intravenous line was established, antiemetic prophylaxis in the form of ondansetron 4 mg and dexamethasone 8 mg were given. Premedication with midazolam 2 mg was given, and the ringer's lactate infusion was started. Elastic stockings were applied to all participants.

All patients received the same GA technique. Induction was done by fentanyl 1 µg/kg, propofol 2 mg/kg, and cisatracurium 0.15 mg/kg. Anesthesia was maintained by end-tidal concentration of sevoflurane 1% in oxygen and air mixture. Injection of cisatracurium 0.03 mg/kg was given as required, and ventilator settings were adjusted to keep end-tidal CO2 ($EtCO_2$) between 35 and 40 mmHg. Fentanyl 1 µg/kg was given when heart rate (HR) or mean blood pressure (MAP) increased more than 20% above the baseline. The intra-abdominal pressure was kept at 12–14 mmHg. After completion of the surgical procedure, all patients received intraperitoneal local anesthetic instillation (100 mg bupivacaine 0.25%) (40 ml) through the trocar. This solution was instilled in the sub-diaphragmatic space and the patients were kept in Trendelenburg's position for 5 min. The patients were divided into three groups:

Group 1: received intravenous infusion of 50 ml normal saline over 10 minutes (Control group).

Group 2: received intravenous infusion of 50 ml normal saline containing dexmedetomidine 1 µg/kg over 10 minutes (IV dexmedetomidine group).

Group 3: received intraperitoneal instillation of dexmedetomidine 1 µg/kg plus 100 mg bupivacaine 0.25% through the trocar, and intravenous infusion of 50 ml normal saline over 10 minutes (IP dexmedetomidine group).

Evacuation of CO2 from the abdomen was done carefully followed by infiltration of the port sites with 10 ml of bupivacaine 0.25% at the end of the surgery. Neuromuscular block was reversed by neostigmine 0.05 mg/kg and atropine 0.02 mg/kg then tracheal extubation was done after fulfillment of the criteria of extubation. All patients were transferred to the recovery room where oxygen supplementation was administrated until achieving an Aldrete score of ≥ 9 before being transferred to the ward. Paracetamol 1 g IV every 6 h and ketorolac 30 mg IV every 8 h were given to all patients.

Extubation time (time from the end of anesthesia till extubation) and recovery time (time elapsed since extubation till Aldrete score ≥9) were noted for all patients. Postoperative pain was recorded for all the patients using VAS pain score at the recovery room, 2, 4, 6, 12, 18, and 24 h. Time to first request of analgesia was recorded, considering the extubation time as "Time 0". Rescue analgesia of tramadol 50 mg IV was considered when VAS ≥ 4. The total consumption of tramadol on the first postoperative day was calculated for each patient. Hemodynamic parameters (heart rate and mean arterial pressure) were recorded before induction of anesthesia and at 30 min interval.

Any side effects, such as hypotension (mean arterial pressure less than 25% of the preoperative value and treated with fluid infusion or ephedrine boluses of 3 mg), bradycardia (heart rate less than 45 beats/min and treated with 0.5 mg of atropine), shoulder pain, nausea, and vomiting, were recorded in the perioperative period. All observations were carried out by a single investigator, who was blinded to the study groups.

The primary outcome was the time to first request of analgesia, and the secondary outcomes were total consumption of tramadol in 24 h, postoperative VAS pain score, the number of patients on rescue analgesia, extubation time, recovery time, Aldrete score, and the incidence of adverse effects, i.e., hypotension, bradycardia, nausea/vomiting, and shoulder pain.

2.1. Sample size

Based on a previous study, [4] sample size calculation revealed that at least 31 patients were required in each group, to detect at least 25% significant reduction in the time to first request of analgesia at 0.05 α value, 95% power of the study, 35 patients will be selected in each group to overcome dropout cases.

2.2. Statistical analysis

The SPSS computer program (SPSS Inc., Chicago, IL, USA) was used in the statistical analysis of the recorded data. Categorical data were presented as number and

percentage (%) and analyzed using the Chi-square test, while parametric data were analyzed by one-way ANOVA test and the post-hoc Tukey's HSD test and expressed as mean ± standard deviation. Kruskal-Wallis test was used for the statistical evaluation of the non-parametric data which were expressed as a median and interquartile range with the intergroup comparison carried out by Mann-Whitney test. The results were considered statistically significant when the *P* value was less than 0.05.

3. Results

A total of 134 patients were evaluated for eligibility, out of whom 105 patients were randomly allocated into three equal groups (Figure 1). Demographic data and the duration of the surgery were comparable between the three groups (Table 1).

Regarding first time of rescue analgesia, the number of patients needed for rescue analgesia, and amount of rescue tramadol analgesia, there were statistically significant differences between the three groups ($P < 0.0001$). IP group had the longest time for rescue analgesia; the least number of patients needed for rescue analgesia, and decreased the amount of rescue tramadol analgesia than the other groups (Table 2).

The comparison of VAS between the three groups was statistically significant at 6, 12, and 18 hours ($P = 0.003$, 0.012, ˂ 0.0001; respectively) (Figure 2). At the 6th postoperative hour, the VAS of IV and IP groups was lower than the control group ($P = 0.006$, 0.002; respectively). At the 12th postoperative hour, the VAS

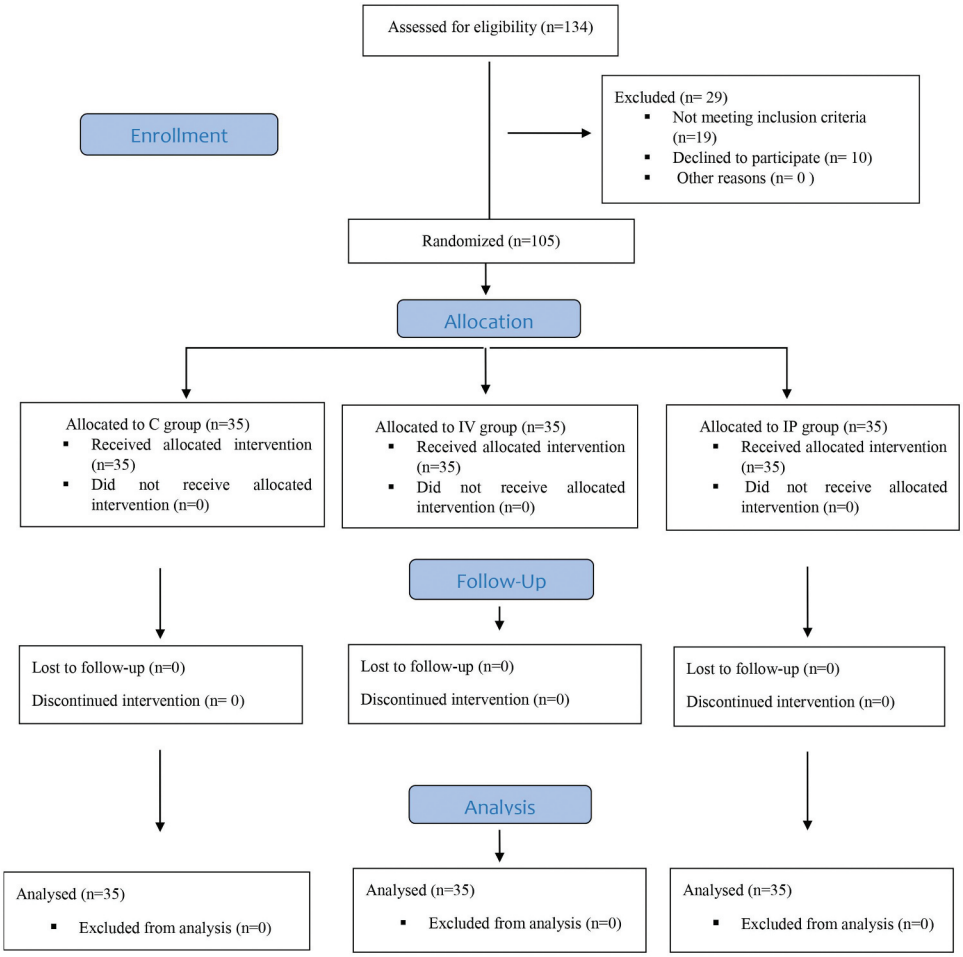

Figure 1. CONSORT flow chart of the three studied groups.

Table 1. Demographic data, and duration of the surgery of the studied groups.

	C Group (n = 35)	IV Group (n = 35)	IP Group (n = 35)	P- value
Age (years)	41.4 ± 12.57	35.86 ± 12.18	42.09 ± 12.63	0.077
BMI (kg/m^2)	42.12 ± 5.49	41.31 ± 4.96	42.87 ± 4.65	0.432
Gender (F/M) (n)	(11/24)	(7/28)	(8/27)	0.515
ASA II /III (n)	(19/16)	(20/15)	(17/18)	0.765
Surgery Time (min)	111.6 ± 17.89	117.06 ± 22.25	113.69 ± 20.09	0.523
Intraoperative rescue fentanyl (mcg)	93.86 ± 9.95	90.97 ± 8.04	94.4 ± 6.02	0.173

Notes: C (control group), IV (intravenous group), and IP (intraperitoneal group). Data expressed as (mean ± SD), or patients' number (n). * Denoted significant difference between the studied groups ($P \leq 0.05$)

Abbreviations: BMI: body mass index. ASA: American society of anesthesiologist.

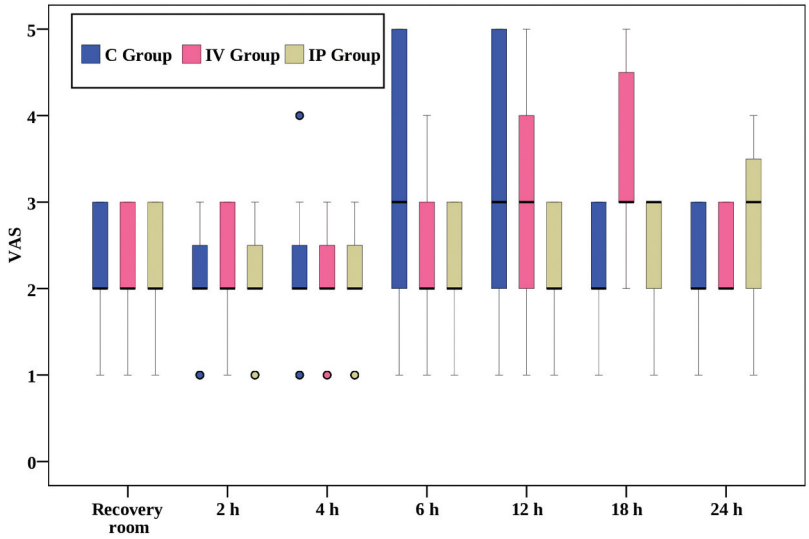

Figure 2. Visual Analog Scale (VAS) of the three studied groups.

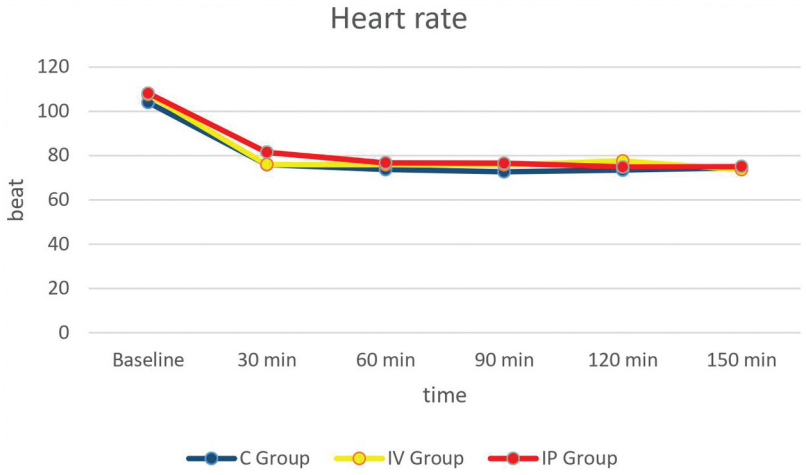

Figure 3. Heart rates of the three studied groups.

Table 2. First time and the amount of rescue analgesia, and the number of patients on rescue analgesia.

	C Group (n = 35)	IV Group (n = 35)	IP Group (n = 35)	P-value	P1-value	P2-value	P3-value
First time of rescue analgesia (min)	357.71 ± 68.31	922.29 ± 332.82	1460 ± 171.81	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*
Amount of rescue tramadol analgesia (mg)	68.13 ± 29.92	40 ± 26.57	15.71 ± 23.55	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*
Number of patients on rescue analgesia (n) (%)	35 (100%)	26 (74.3%)	11 (31.4%)	< 0.0001*	0.001*	< 0.0001*	< 0.0001*

Notes: C (control group), IV (intravenous group), and IP (intraperitoneal group). Data expressed as (mean ± SD), or patients number (percentage). *Denoted significant difference between the studied groups (P ≤ 0.05). P value presented the comparison between the three groups. P1 value presented the comparison between C group and IV group. P2 value presented the comparison between C group and IP group. P3 value presented the comparison between IV group and IP group.

of IP group was lower than control and IV groups (P = 0.006, 0.043; respectively). At the 18th postoperative hour, the VAS of IP and control groups was lower than IV group (P ˂ 0.0001, ˂ 0.0001; respectively). At the recovery room, 2nd, 4th, and 24th postoperative hours, the VAS was comparable between the three groups.

The comparison of HR and MAP between the three groups was statistically insignificant (Figures 3 & 4).

Extubation time between the three groups was statistically significant (P < 0.0001) (Table 3). Regarding the recovery time, there was a statistically significant difference between the three groups (P < 0.0001) (Table 3). Comparing the Aldrete score between the three groups was statistically significant (P = 0.022) (Table 3). The incidence of complications between the three groups was comparable (P = 0.613) (Table 3).

4. Discussion

Laparoscopic sleeve gastrectomy has become a popular procedure used for the management of obesity over the last several years. Pain after laparoscopic surgeries has three mechanisms: parietal pain;

Table 3. Extubation and recovery times, Aldrete score, and the incidence of complications of the studied groups.

	C Group (n = 35)	IV Group (n = 35)	IP Group (n = 35)	P-value	P1-value	P2-value	P3-value
Extubation time (min)	8.83 ± 2.14	14.06 ± 4.74	9.8 ± 2.92	< 0.0001*	< 0.0001*	0.24	< 0.0001*
Recovery time (min)	17.26 ± 5.43	24.46 ± 6.86	16.46 ± 5.28	< 0.0001*	< 0.0001*	0.572	< 0.0001*
Aldrete score	9 (9–10)	9 (7–10)	9 (9–10)	0.022 *	0.024*	0.81	0.015*
Incidence of Complications							
• PONV	3 (8.6%)	3 (8.6%)	2 (5.7%)	0.613			
• Shoulder pain	4 (11.4%)	4 (11.4%)	4 (11.4%)				
• Hypotension	-	2 (5.7%)	1 (2.9%)				
• Bradycardia	-	4 (11.4%)	-				

Notes: C (control group), IV (intravenous group), and IP (intraperitoneal group). PONV: postoperative nausea and vomiting. Data expressed as (mean ± SD), patient number (percentage), or median (interquartile range). *Denoted significant difference between the studied groups (P ≤ 0.05). P value presented the comparison between the three groups. P1 value presented the comparison between C group and IV group. P2 value presented the comparison between C group and IP group. P3 value presented the comparison between IV group and IP group.

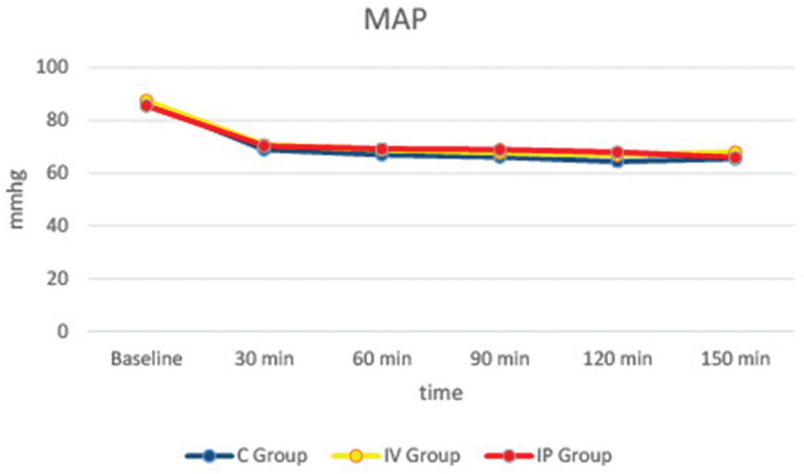

Figure 4. Mean Arterial Blood pressure (MAP) of the three studied groups.

that results from the surgical incision of the abdominal wall for the port insertion; visceral pain; due to dissection of the stomach and stretching of intra-abdominal tissue from intra-peritoneal CO_2 insufflation; and shoulder pain; which is referred pain from diaphragmatic nerves irritation due to carbonic acid that is produced from CO2 in the peritoneal cavity. The challenge of postoperative pain control has a particular interest. [5]

The main finding that emerged from our study showed that IP administration of dexmedetomidine as an adjuvant to IP bupivacaine is as efficacious as IV administration of dexmedetomidine along with IP bupivacaine alone. The rationale of IV dexmedetomidine prolong the peripheral nerve block has been evaluated in previous studies. On intergroup analysis, the first statistically significant difference was observed in IV dexmedetomidine and IP dexmedetomidine when compared to the control group at 6 h postoperatively; this may be explained by wearing off of bupivacaine effect. Whereas the significant difference between IV dexmedetomidine and IP dexmedetomidine at 12 h postoperatively can be explained by prolongation of action of bupivacaine by adding dexmedetomidine.

The first time of rescue analgesia was prolonged in IP dexmedetomidine (1460 ± 171.81 min) compared to IV dexmedetomidine (922.29 ± 332.82 min) and control group (357.71 ± 68.31 min). The total amount of rescue tramadol was lower in IP dexmedetomidine (15.71 ± 23.55 mg) compared to IV dexmedetomidine (40 ± 26.57 mg) and control group (68.13 ± 29.92).

Installation of LA intraperitoneally has been considered as an important method to reduce postoperative pain following laparoscopic surgery. Also, it decreases the incidence of shoulder pain, nausea, vomiting, and hospital stay. [6,7] It exhibits analgesia by blocking free nerve endings in the peritoneum and inhibiting the release of prostaglandins that stimulate nociceptors. Moreover, LA absorption through the peritoneal surface may enhance analgesia by reducing nociception. [8]

Dexmedetomidine is an α_2-adrenoceptor agonist, which has been associated with prolonged duration of the local anesthetic when injected perineural, [9,10] neuro-axial [11], or intravenous. [12] It has an analgesic effect through centrally mediated α_2 receptors at the spinal and cerebral levels. It prolongs the duration of the nerve block after administration in the peritoneal cavity by blockade of hyperpolarization-activated cation channels preventing the release of substance

P. [13] A possible mechanism of prolonged duration of analgesia is local vasoconstriction, thus increasing the concentration of local anesthetics around the nerve producing anti-nociceptive effect. [14] Also, some studies suggest that dexmedetomidine has local anesthetic effects through inhibition of nerve impulse conduction along C and A_δ fibers, not through α_2 action. [15] After perineural administration of dexmedetomidine, it is absorbed and redistributed to produce its systemic effects.

The possible explanations of the prolonged duration of analgesia in the IP group of dexmedetomidine more than the IV group are as follows: in the IP group, dexmedetomidine exerts its mechanism of action centrally through systemic absorption, and perineurally through higher concentration around the nerve, which differs from the IV group that has only a central mechanism of action.

In agreement with our results, a study was conducted by Elnabtity and Ibrahim [8], who evaluated the analgesic effects of adding dexmedetomidine 1 μg/kg to intraperitoneal bupivacaine after laparoscopic appendectomy in children. They showed lower VAS with increased time to first rescue analgesia and decreased postoperative pethidine requirements in dexmedetomidine group compared to bupivacaine alone.

Also, Oza et al. [16] observed results similar to our study. They revealed significantly low VAS after 12 h postoperatively in dexmedetomidine added to bupivacaine intraperitoneal compared to bupivacaine alone after laparoscopic surgery. The duration of analgesia was longer in dexmedetomidine group (14.5 ± 1.86 h) than bupivacaine group (13.06 ± 1.09 h) and higher number of rescue analgesic doses in bupivacaine group (2.56 ± 0.20) than dexmedetomidine-bupivacaine group (1.76 ± 0.16).

Moreover, Fares et al. [17] concluded that adding 1 μg/kg dexmedetomidine to intraperitoneal bupivacaine enhances the analgesic quality and prolongs the duration of postoperative analgesia compared to bupivacaine alone in laparoscopic colorectal cancer surgery. This was in agreement with our results. Shukla et al. [18] reported a significant reduction in the total analgesic consumption postoperatively with a longer time for rescue analgesia when comparing dexmedetomidine to tramadol added to bupivacaine intraperitoneally in laparoscopic cholecystectomy. VAS was significantly lower in IP dexmedetomidine group compared to control and tramadol group during the first 24 h. Similar results were described by Narasimham and Rao. [19].

A previous study [20] has assessed the sedative effect of IV dexmedetomidine during spinal anesthesia; they reported significant prolongation of the duration of postoperative analgesia and decreased consumption of the postoperative opioids. Also, another study [21] evaluating the effects of IV dexmedetomidine on interscalene brachial plexus block concluded the same results.

Abdullah et al. [12] concluded that adding dexmedetomidine either perineural or intravenous prolongs the duration of interscalene brachial plexus block.

In their study Sivakumar et al. [22] compared perineural versus intravenous dexmedetomidine as a local anesthetic adjuvant in ultrasound-guided fascia iliaca compartment block for femur surgeries, and concluded prolonged duration of analgesia with reduced 24 h postoperative morphine consumption in the perineural group.

However, the results of the study conducted by Chilkoti et al. [7] were against ours. They showed that the mean time to the first analgesic requirement was prolonged in the IV dexmedetomidine group (210 ± 161.17 min) than IP dexmedetomidine group (90.80 ± 80.46 min) and control group (59.68 ± 71.05 min). Also, the total consumption of tramadol was the lowest in the IV group followed by the IP group than control group. This difference may be related to the low dose of dexmedetomidine 0.5 μg/kg versus dexmedetomidine 1 μg/kg in the present study.

Thakur et al. [23], in their study comparing IV dexmedetomidine and IP dexmedetomidine added to IP levobupivacaine versus IP levobupivacaine alone, reported lower pain scores in the three groups till 4 h postoperative, and there was no significant difference between IV dexmedetomidine and IP dexmedetomidine up to 8 h. Afterwards, the pain scores were lower in IV dexmedetomidine. They disagreed with the results of the present study.

Regarding the hemodynamic parameters, the intergroup analysis showed no significant difference after the start of the surgery, injection of the study drugs, and postoperative. However, there was a decrease in the heart rates and the blood pressure in IV and IP dexmedetomidine groups, but this was statistically insignificant. Also, dexmedetomidine attenuates the hemodynamic response to tracheal extubation. Injection of a single dose of dexmedetomidine 1 μg/kg either IV [24] or IP [17] is associated with stable hemodynamics. Slow infusion of dexmedetomidine over 10 min in the IV group produces minimal effects on hemodynamics.

The extubation time, besides the recovery time, was found statistically significantly longer in IV dexmedetomidine group than IP dexmedetomidine compared to control group. It is likewise attributed to the sedative effect of dexmedetomidine. It could be related to altered pharmacokinetics in the obese patients. Also, starting the infusion after completion of the surgery, before awaking of the patient, and a relatively long half-life of dexmedetomidine. This leads to delayed time to discharge from recovery room in IV dexmedetomidine group compared to IP dexmedetomidine and control group.

Sedation related to dexmedetomidine is induced by activation of alpha 2 adrenoceptors in the locus coeruleus which leads to a sedative state that resembles natural sleep. Therefore, it keeps the patients easily arousable without the risk of airway obstruction and respiratory depression. [25] Chilkoti et al. [7] observed higher level of sedation in IV dexmedetomidine compared to IP dexmedetomidine and control groups. It was significant in the first 2 h postoperatively. Thakur et al. [23] reported the same significant difference but up to 4 h.

Prolonged recovery times were reported by Abdel-Rahman et al. [26] when they administered dexmedetomidine to decrease the incidence of emergence agitation before emergence from general anesthesia. Ohtani et al. [27] suggested that delayed recovery occurred due to co-administration of dexmedetomidine with propofol for total IV anesthesia.

The parameters of recovery profiles were longer in dexmedetomidine group compared to control group, with no significant difference in a study conducted by Mostafa et al. [28] However, Bhattacharjee et al. [29] showed that dexmedetomidine does not prolong the recovery time. Also, in their study Indira et al. [30] concluded smooth extubation, recovery, and acceptable sedation level of the patients.

Adverse effects such as hypotension, bradycardia, shoulder pain, nausea, and vomiting show no significant difference between the three groups. This goes with the results reported by Shukla et al., [18] and Fares et al. [17]

The incidence of shoulder pain was lower in all groups, and it may be attributed to the Trendelenburg's position which prolongs the contact time of the local anesthetics with the diaphragm, the stomach, and the stapler lines.

5. Limitations of this study

We did not measure the peak plasma level of dexmedetomidine in bariatric patients after intraperitoneal and intravenous injection. Further studies are required to detect the appropriate dose of dexmedetomidine, timing of injection, and routes of administration to provide the best pain relief with minimal side effects postoperatively in obese patients undergoing laparoscopic sleeve gastrectomy. Also, we did not report the comorbidities with the demographic data.

6. Conclusion

Intraperitoneal administration of dexmedetomidine as an adjuvant to intraperitoneal bupivacaine is as efficacious as intravenous administration of dexmedetomidine compared to intraperitoneal administration of bupivacaine alone. However, the intraperitoneal administration has the longest duration of analgesia and the least postoperative analgesic consumption.

Disclosure statement

The authors declare no competing interests.

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