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Comparison of Intraperitoneal Instillation of Bupivacaine and Bupivacaine with Dexmedetomidine for Postoperative Analgesia after Laparoscopic Surgery

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Abstract:

Background and aims: *Post-operative pain is one of the major problems in laparoscopic surgeries, wherein lack of control on it has many side-effects such as tachycardia, hypertension, myocardial ischemia, decreased alveolar ventilation, and prolongs hospital stay. We have evaluated the antinociceptive effects of intraperitoneal instillation of bupivacaine plain and bupivacaine with dexmedetomidine in patients undergoing laparoscopic surgeries.*

Materials: *A total of 100 patients belonging to American Society of Anesthesiologist physical status I-II, in the age group of 18-70 years, of either sex undergoing laparoscopic surgery under general anesthesia were divided in two groups. Group B received bupivacaine (0.25%) 40 ml intraperitoneal instillation and group BD received bupivacaine (0.25%) 40 ml with dexmedetomidine 1μg/kg intraperitoneal instillation before removal of trocar at the end of surgery. The quality of analgesia was assessed by visual analogue scale (VAS) and sedation by Ramsey sedation score. Time to first request of analgesia, total dose of analgesic in first 24 hrs and adverse effects were also noted.*

Results: *There was statistically significant difference in VAS at six hours after surgery in group BD (3.14±0.40) compared to group B (4.12±0.82) up to 24 hours with higher sedation score for first six hours. The time to first rescue analgesic was significantly higher in group BD (7.76 hours) compared to group B (5.92 hours) and less total analgesic consumption(mg) in group BD (1.9) compared to group B (2.21).*

Conclusion: *Intraperitoneal instillation of bupivacaine with dexmedetomidine significantly prolong the duration of analgesia as compared to intraperitoneal instillation of bupivacaine alone without any side effects.*

Keywords: ***Bupivacaine hydrochloride, dexmedetomidine hydrochloride, intraperitoneal instillation, postoperative pain, visual analogue scale.***

1. Introduction:

Different type of abdominal and gynecological surgeries are done laparoscopically by using two or more ports which produce surgical trauma and moderate to severe pain. Intraperitoneal insufflations of gases like CO_2 stretch the abdominal tissues and diaphragmatic irritation caused by residual carbon dioxide in the peritoneal cavity causing peri-operative pain. Pain may be visceral, shoulder tip or parietal. [1, 2, 3]

Intensity of pain is more, immediately after surgery and less after twenty four hours. Methods used for postoperative pain relief after laparoscopic surgery include non-steroidal anti-inflammatory drugs, parenteral opiods, intraperitoneal instillation of local anaesthetics, alone or in combination with opioids, alpha-2 agonist's dexmedetomidine etc. [3, 4, 5, 6, 7, 8]

The aim of this study was to compare the antinociceptive effects intraperitoneal instillation of bupivacaine plain and bupivacaine with dexmedetomidine in patients undergoing laparoscopic surgeries.

2. Methods:

This prospective, randomized, double-blind study was designed to include 100 adult patients (18–70 yr) of either sex, ASA risk I and II, undergoing laparoscopic cholecystectomy, laparoscopic appendicectomy, diagnostic laparoscopy under general anaesthesia. The study protocol was approved from Local Institutional Ethical Committee and written informed consent was obtained from all the patients. Patients with impaired kidney function, history of drug or alcohol abuse, history of chronic pain or daily intake of analgesics, allergic to local anaesthetic, patients who are

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not able to appreciate the VAS score, uncontrolled medical disease (diabetes mellitus and hypertension), and history of intake of non-steroidal anti-inflammatory drugs or steroids within 24 h before surgery were excluded from the study.

Before taking the patient to the operation theatre, he/she was explained the numeric VAS (Visual Analogue Scale) score for pain (VAS score 0-no pain, 10-worst possible pain). After arrival in operating room, routine monitors in the form of electrocardiogram (ECG), non-invasive blood pressure measurement (NIBP), pulse oxymetry (SpO_2) were applied and 18 gauge intravenous cannula was inserted into a suitable vein on the dorsum of non-dominant hand. The patient was premedicated with glycopyrrolate inj. (4 µg /kg), ondansetron inj. (150 µg /kg) and fentanyl inj. (2 µg /kg) intravenously. The patient was then pre-oxygenated through a face mask with 100 % oxygen for 3 min. The induction was done with propofol 2 mg/kg intravenously and to facilitate the endotracheal intubation, succinylcholine inj. 2mg/kg was given intravenously. The patient was intubated with a suitable size portex cuffed endotracheal tube. Throughout the procedure controlled ventilation was maintained with 100% O_2, sevoflurane (1-2%) and vecuronium bromide. Intraoperative monitoring included ECG, NIBP, SpO_2, end tidal carbon dioxide ($ETCO_2$) and Temperature. All operations were performed by using either a 3 port technique or a 4 port technique which involved direct visual access to the peritoneum, insufflations with CO_2, no irrigation, and no drainage. Ventilation was adjusted to maintain $ETCO_2$ between 35-40 mm of Hg whereas intra-abdominal pressure was maintained between 12-14 mm of Hg. During intraoperative period all patients received ringer lactate and dextrose normal saline at the rate of 5-7 ml/kg/hr. All patients were instilled with 40 ml of solution in a standardized manner by the operating surgeon under visual control before removal of trocar at the end of the surgical procedure. Group B received 40 ml (0.25%) bupivacaine and group BD received 40 ml (0.25%) bupivacaine with dexmedetomidine (1 µg /kg). The drugs were prepared and given to the investigator who was blind to the identity of drugs. CO_2 was then evacuated from the peritoneal cavity and skin incisions were sutured. Neuromuscular blockade was reversed with glycopyrollate 8µg/kg and neostigmine 0.05mg/kg intravenously. Extubation was done after proper oral and endotracheal suctioning. Patients were shifted to the post-operative recovery room when they were breathing spontaneously and following verbal command with stable vital parameters. Postoperative pain was assessed using numeric VAS 0 - 10 cm. When the VAS pain score was equal or more than 4, the patients were given inj. diclofenac sodium as a rescue analgesic in the dose of 2 mg/kg intravenously slowly. The severity of PONV was graded on a four-point ordinal scale (0- no nausea or vomiting; 1-mild nausea; 2- moderate nausea; and 3- severe nausea with vomiting). Rescue antiemetic ondansetron 4 mg intravenously was given to all patients with PONV of grade ≥2. The following parameters were evaluated in all study groups: (1) Time to first request of analgesia (time elapsed between extubation and first request for analgesic dose), (2) The incidence and severity of postoperative pain for 24 h (the severity of postoperative pain measured at 1, 2, 4, 6, 8, 12, 16, 20 and 24 hrs. postoperatively, using VAS pain score, (3) total dose of analgesia (4) Postoperative complications (5) Postoperative haemodynamics (pulse, blood pressure) (6) Comparative sedation score.

Data were expressed as mean ± standard deviation, number and percentage (%).Categorical variables were analyzed using chi-square with yate's correction and Fisher's exact test (two tailed) as appropriate. Continuous variables were tested using an unpaired student's *t*-test. Statistical calculations were carried out using Microsoft Office Excel Software (Microsoft 2007, Computer Software) and Graph Pad Prism 6.05 (quickcalc) Software. P value of less than 0.05 was considered statistically significant.

3. Results:

There was no significant difference with respect to age, weight, sex, duration of surgery, type of surgery among two groups. [Table 1, 2]

Table 1 Demographic data

Patients Characteristic	Group B (N=50)	Group BD (N=50)	P Value
Age (year)	33.90±10.44	34.8±10.01	0.66
Sex (male/female)	13/37	15/35	0.823
Body Weight (kg)	53.42±6.60	55.18±7.19	0.20
ASA* grade I/II	30/20	25/25	0.4215
Duration of Surgery(min)	47.5 ±13.82	48.8±13.91	0.64

*ASA-American Society of Anesthesiologist

Data presented as mean ± standard deviation or Number: *P value < 0.05 is considered significant

Table 2 Types of surgeries

Surgical Procedures	Group B (N=50)	Group BD (N=50)	P Value
Cholecystectomy	20(40%)	20(40%)	1.0
Appendicectomy	20(40%)	20(40%)	
Diagnostic laparoscopy	10(20%)	10(20%)	

Data presented as Number or percentage: *P value < 0.05 is considered significant

Sedation score was higher in group BD compared to group B according to Ramsey Sedation score. It was clinically significant in group BD from 1 hour to 6 hour compared to group B. [Table 3]

Table 3 Ramsey sedation score

Ramsey Sedation Score	
1	Patient is anxious and agitated or restless, or both
2	Patient is co-operative, oriented and tranquill
3	Patient is respond to command only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response

Mean pain scores were significantly lower in the group BD when compared to group B during the entire duration of the study. The duration of analgesia was 3 to 6 hours for group B and 7 to 10 hours for group BD. There was statistically significant difference in VAS pain score at six hours after surgery in group BD (3.14±0.40) compared to group B (4.12±0.82) up to 24 hours. [Table 4]

Table 4 VAS postopertive period up to 24 hrs

Time (Duration)	Group B	Group BD	P Value
1 hrs.	1.40±0.53	1.32±0.51	0.44
2 hrs.	1.98±0.38	1.92±0.34	0.40
4 hrs.	2.80±0.53	2.66±0.47	0.16
6 hrs.	4.12±0.82	3.14±0.40	<0.0001*
8 hrs.	2.26±0.66	4.04±0.88	<0.0001*
12 hrs.	2.94±0.24	2.12±0.33	<0.0001*
16 hrs.	3.46±0.73	2.96±0.40	<0.0001*
20 hrs.	4.28±0.90	3.90±0.46	0.009*
24 hrs.	2.94±0.74	2.30±0.51	<0.0001*

Data presented as mean ± standard deviation: *P value < 0.05 is considered significant

Regarding the pattern of pain, it was predominantly of generalized abdominal pain among both groups followed by shoulder pain. None of the patients complained of incision pain. [Table 5]

Table 5 Pattern of pain

Types of pain	Group B	Group BD	P Value
Shoulder	7(14%)	6(12%)	0.766
Generalized abdominal	15(30%)	6(12%)	0.027*
Incisional	8(16%)	8(16%)	1.0
Total	30(60%)	20(40%)	0.045*

Data presented as number or percentage: *P value < 0.05 is considered significant

Time to requirement of first dose rescue analgesia was prolong in the group BD(7.76 hours) compared to group B (5.92 hours), indicating better and longer pain relief in the group BD compared to groups B. Total analgesic consumption was more in group B (2.21) compared to group BD (1.9). [Table 6]

Table 6 Analgesic requirement

Analgesic profile	Group B	Group BD	P Value
No. of patients given rescue analgesic	30(60%)	20(40%)	0.045*
Mean time for first dose(hours)	5.92±0.69	7.76±0.65	<0.0001*
Mean total dose	2.21±0.41	1.9±0.36	0.0001*

Data presented as mean ± standard deviation or number: *P value < 0.05 is considered significant

The incidence of nausea and vomiting was similar and there was no significant difference in both groups. [Table 7]

Table 7 Side effects

Adverse event	Group B	Group BD	P Value
Nausea	5(10%)	4(8%)	0.726
Vomiting	2(4%)	2(4%)	1.0
Pruritus	0	0	
Excessive sedation	0	0	

Data presented as number or percentage: *P value < 0.05 is considered significant

Figure 1 Changes in pulse rate at different time interval. There was statistically significant difference between two groups of patients in terms of pulse rate all the time except at 20 hour. Data presented as mean.

Figure 1

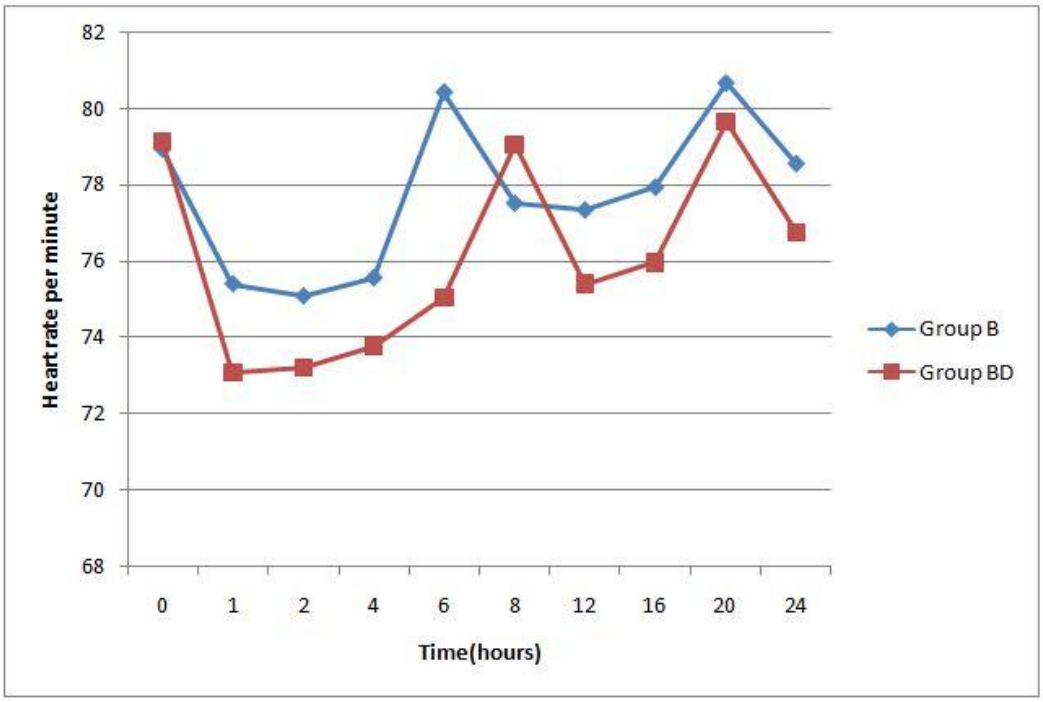


Figure 2 Changes in systolic blood pressure at different time interval. There was statistically significant difference between two groups of patients in terms of systolic blood pressure from 1 hour to 12 hours. Data presented as mean.

Figure 2

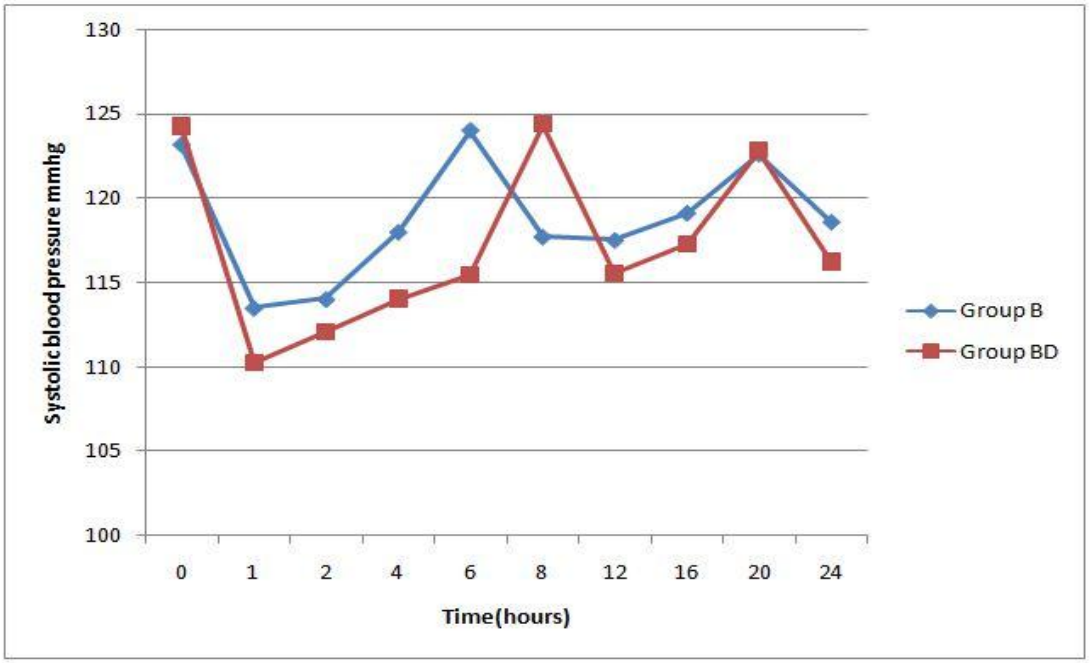
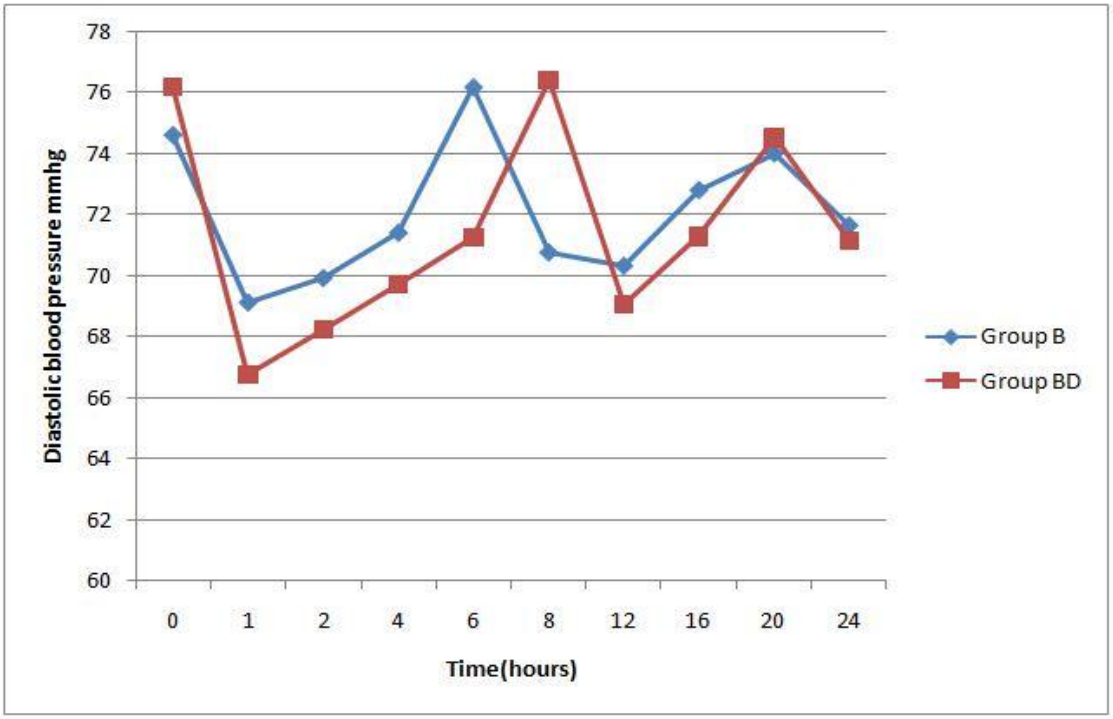


Figure 3 Changes in diastolic blood pressure at different time interval. There was statistically significant difference between two groups of patients in terms of diastolic blood pressure from 1 hour to 12 hours. Data presented as mean.

Figure 3



4. Discussion:

Laparoscopic surgery, also called minimally invasive surgery is a modern surgical technique used for various surgeries like cholecystectomy, appendicectomy, hernia repair. Pain after laparoscopic surgery is due to skin incision site, creation of pneumoperitoneum, trauma created by surgical procedure. [1]

Postoperative pain after laparoscopic surgery are mainly due to stretching of intraabdominal cavity(visceral pain), phrenic nerve irritation by residual carbon dioxide in the peritoneal

cavity (shoulder pain) and surgical incision (parietal pain).[2]

Intraperitoneal instillation of local anaesthetic has become a popular practice for pain relief after laparoscopic surgery. Intraperitoneal local anaesthetic is likely to blockade free afferent nerve endings in peritoneum. Systemic absorption of local anaesthetic from the peritoneal cavity may also play a part in reduced nociception although this would expect to occur after any local anaesthetic technique. [1, 3, 4]

As pain after laparoscopic surgery is multifactorial and multimodal analgesia is necessary to counter this pain. Dexmedetomidine is a potent and more selective alpha-2 agonist and reduces pain scores after laparoscopic cholecystectomy with multimodal analgesia. [5]

Use of dexmedetomidine alpha-2 agonist as an adjuvant in laparoscopic surgery is deemed to be safe, improve patient's comfort, shorten the length of stay in the post operative care unit and decrease the total analgesic requirement in the ward. [5, 8]

Intraperitoneal instillation of 20 ml of 0.5% bupivacaine provides effective analgesia and intraperitoneal instillation of 100 mg bupivacaine did not cause toxicity. This technique is safe with good pain relief in initial few hours. [6]

Bupivacaine has more potent and prolonged duration of action. The half life of bupivacaine is between 5 and 16 hours. We have used 100 mg bupivacaine and none of patients developed any signs of toxicity.

In our study, we found less VAS score for pain in group BD than group B. Chudrigar *et al*. and Maharjan *et al*. had done the same study in laparoscopic cholecystectomy and they found less VAS score in study group patients for 3 hours. [7, 10]
In our study, the mean pain score of group BD was 3.14±0.40 and group B was 4.12±0.82 at six hour respectively. This difference is suggestive of prolong duration of analgesia by adding dexmedetomidine with bupivacaine.

There was no difference in shoulder pain in both groups in our study. Butala *et al.* have found that no shoulder pain in patients because of the residual intraperitoneal CO_2 was emptied carefully by the surgeon. [3]

In our study, the mean duration of analgesia was 3 to 6 hours for group B and 7 to 10 hours for group BD. Chudrigar *et al*. had found the mean duration of analgesia lasting for 2-8 hours. [7]

Gupta and colleagues observed the combination of intraperitoneal bupivacaine with fentanyl provided better pain relief than bupivacaine alone [9] and Butala *et al.* concluded that the combination of intraperitoneal bupivacaine with morphine is superior to the plain bupivacaine for the relief of postoperative pain in patients undergoing laparoscopic gynecological surgery without any significant adverse events.[3]

Intraperitoneal instillation of local aneasthetic, to reduce pain after laparoscopic cholecystectomy.[11,12,13] and intraperitoneal instillation of bupivacaine decrease postoperative pain with hasten return of bowel function and reduce postoperative analgesic requirement in laparoscopic gynecological surgery.[14,15]

In our study, comparing the analgesic requirements showed that a number of patients who needed rescue analgesia is significantly lower in group BD compared to group B. Time for the first analgesic dose was significantly prolonged and total analgesic doses required was significantly less in group BD compared to group B.

Intraperitoneal bupivacaine for laparoscopic chlecystectomy reduces pain without adverse effects and may become a routine practice. [16, 17].

Regarding adverse effects, only nausea and vomiting was found in 13 out of 100 patients and was equally distributed in both groups. There was no pruritus or excessive sedation in group BD patients.

Vital parameters like heart rate, blood pressure are important indicators of patients comfort as the values correlated well with high VAS scores.

Conclusion:

We concluded that intraperitoneal instillation of dexmedetomidine with bupivacaine produces prolonged duration of analgesia and require less number of analgesic doses compared to bupivacaine alone in patients undergoing laparoscopic surgery without any significant side effects.

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