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Comparison of Post-Operative Analgesia in Laparoscopic Surgeries with Intraperitoneal Dexmedetomidine with Bupivacaine and Bupivacaine Alone

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Abstract

Background: Though laparoscopy is associated with lesser postoperative pain, it is not completely a pain free procedure. Given the expanding role of ambulatory surgery and need to facilitate an earlier hospital discharge, improving postoperative pain control has become an important issue for anesthesiologists. *Objective:* To analyze the analgesic effect of intraperitoneal instillation of 1 µg/kg dexmedetomidine with 0.25% bupivacaine to that of 0.25% bupivacaine alone in patients undergoing laparoscopic surgeries. *Methods:* Sixty patients posted for elective laparoscopic surgeries were randomized into two groups - Group B: received 30 ml Bupivacaine 0.25%, Group BD: received 30 ml of mixture of Bupivacaine 0.25% with Dexmedetomidine (1 µg/kg), intraperitoneally before removing the trocar. The intensity of the pain was assessed using Visual Analog scale (VAS) at 30 min, 1 hour, 2 hours, 6 hours, 12 hours, and 24 hours. The duration of analgesia, demand for rescue analgesics and side effects, if any were noted. *Results:* The demographic variables were comparable. There was a significantly prolonged duration of post-operative analgesia, a significant reduction in VAS scores and analgesia requirement rate over the 24-hour period in Group BD. Though the heart rate decreased significantly in patients of dexmedetomidine group, they were hemodynamically stable. There was no significant difference in the incidence of adverse effects. *Conclusion:* The intraperitoneal instillation of Bupivacaine with 1 µg/kg of dexmedetomidine in laparoscopic surgeries is a better choice for postoperative analgesia with minimal side effects.

Keywords: Laparoscopic Surgeries; Intraperitoneal instillation; Bupivacaine; Dexmedetomidine; Visual Analog Scale; Postoperative Analgesia.

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Introduction

The smaller incisions, lower rates of postoperative complications, faster recovery, early discharge and earlier return to normal activities and work have made laparoscopic procedures the most admired and accepted technique in the recent past [1]. Although laparoscopy is associated with lesser postoperative pain and smoother recovery than open laparotomy, it is not completely a pain

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free procedure [2]. Laparotomy results mainly in parietal pain (abdominal wall), whereas patients complain more of visceral pain after operative laparoscopy [2,3]. There is marked inter individual variation in pain following laparoscopy and the reason remains unclear.

Given the expanding role of ambulatory surgery and need to facilitate an earlier hospital discharge, improving postoperative pain control has become an important issue for anesthesiologists. Various methods have been tried for postoperative analgesia in laparoscopic surgeries like epidural catheters, intramuscular or intravenous opioids, and instillation of local anesthetic solutions intraperitoneally by different authors with varying results [4-9]. The different surgical methods to diminish the pain include low-pressure pneumoperitoneum, local wound infiltration, saline washout, use of warmed, humidified gases and a gasless technique for creating working space.

The improved understanding of the origin of abdominal and shoulder pain after laparoscopic procedures had lead to the use of intra peritoneal instillation and port site infiltration of local anesthetic to reduce post operative pain. The employment of this technique during laparoscopic cholecystectomy and other laparoscopic surgeries under general anesthesia had been investigated in several studies and most of them had revealed significant reduction in the postoperative pain. Most of these studies have been on either one of the commonly used local anesthetic agents in different concentrations.

Dexmedetomidine is a highly selective α_2 adrenergic agonist and its presence in dorsal horn of the spinal cord and in locus coeruleus of brain stem modulates the release of substance P and produces its analgesic effect [10]. Not many studies are available in literature assessing the efficacy of the intra peritoneal instillation of local anaesthetic solutions with dexmedetomidine for postoperative pain relief following laparoscopic surgeries.

Hence this study was designed to compare the efficacy of intraperitoneal instillation of dexmedetomidine with bupivacaine with that of bupivacaine alone on postoperative pain relief in patients undergoing laparoscopic surgeries.

Materials and Methods

After obtaining approval from institutional ethics committee, this prospective, randomized, double blind, comparative study was conducted on sixty patients undergoing elective laparoscopic surgical procedure in a teaching institution from December 2016 to January 2018. Randomization was done using Sealed Envelope technique. The written informed consent was obtained from all these patients prior to their participation in this study.

Inclusion criteria

1. Age group of 18 – 60 years
2. Both sex
3. American society of Anesthesiologists (ASA) physical status I or II

Exclusion criteria:

1. Patient refusal
2. Hypersensitivity to the study drug
3. History of previous abdominal surgeries
4. Significant cardiac and pulmonary disease
5. Patient on beta blocker therapy
6. Pregnant or lactating women

Procedure

Prior to the day of surgery, anesthesiologists had evaluated all patients and explained about the anesthesia process and Visual analogue scale (VAS). ASA fasting guidelines were followed. All the patients were premedicated orally with Tab. Ranitidine 150 mg, Tab. Metoclopramide 10 mg and Tab. Alprazolam 0.25 mg the night before surgery. After arrival to the operation Room, Pulse oximetry (SpO_2), twelve-lead ECG (leads II and V5) for heart rate (HR) and ST segment changes, and non-invasive blood pressure monitors were attached and baseline readings were recorded. The intravenous access with 18G cannula was secured in the non-dominant hand of the patients. All patients were administered Inj. Ondansetron 4 mg, Inj. Glycopyrrolate 0.2 mg and Inj. Fentanyl 2 µg/kg intravenously (i.v) and were preoxygenated for three minutes.

Induction was done with Propofol 2 mg/kg i.v; Tracheal intubation was facilitated using inj. Vecuronium 0.1 mg/kg. Maintainenance of anesthesia was achieved with Halothane 1% along with admixture of Nitrous oxide and Oxygen (2:1) and additional doses of Vecuronium 0.01 mg/kg whenever necessary. The capnogragh was attached. Two experienced laparoscopic surgeons operated on all the laparoscopic cases. Supplementation of Fentanyl 0.5 µg/kg IV was given, whenever necessary.

The anesthesiologist not involved in the study prepared the drug solution. At the end of the procedure, the standard suction-irrigation device (with 10 ml syringe attached) was introduced through the umbilicus port, directed towards the under surface of diaphragm and the study drug was sprayed. The group B patients received 30 ml of 0.25% Bupivacaine whereas Group BD patients received 30 ml of 0.25% Bupivacaine with 1 µg/kg of Dexmedetomidine. At the end of the surgery, the residual neuromuscular blockade was reversed with Neostigmine 0.05 mg/kg and glycopyrolate 0.01 mg/kg. The patients in both the groups were extubated once they are awake, hemodynamically stable and demonstrated adequate breathing and muscle power.

Further assessment was done in the postoperative room by the anesthesiologist blinded to the study groups. The intensity of the pain was assessed using VAS at 30 min, 1 hour, 2 hours, 6 hours, 12 hours, and 24 hours. Where zero score corresponds to 'no pain' and 10 corresponds to the 'maximum' or 'worst pain'. The VAS score ≥ 4 was taken as cut-off for analgesic supplementation. The patients were aware that the scale served to analyze the intensity of pain alone, including shoulder tip and is not a representation of generalized postoperative discomfort. The heart rate, systolic blood pressure and diastolic blood pressure, and oxygen saturation were also assessed and documented at the above times.

Inj. Diclofenac (1 mg/kg) was given slow intravenously to the patients on demand for postoperative analgesia. The time of demand in hours after surgery were noted. Similarly the requirement of repeated doses of analgesia if any were noted and recorded. The side effects like nausea, vomiting, sedation, diarrhoea, urinary retention, shivering, if any were noted.

Statistical Analysis

Data was analysed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 17 and p-value less than 0.05 was considered statistically significant. Microsoft Excel 2013 was used for generating charts and diagrams. Data are shown as mean ± standard deviation and in absolute numbers or percentages. Independent-Samples t-test was used to compare the means between two groups. The Chi square test was used for comparing qualitative parameters. The Multinomial Logistic Regression Analysis was applied to find the relationship between dependent and independent factors.

Observation and Results

The age and sex distribution of patients were similar in both the groups (Table 1). The mean age of patients in group B and BD were 38.1 ± 14.78 years and 36.8 ± 11.42 years respectively and were comparable. The majority of the patients in this study were in the age group of 31-50 years. There was no significant difference in the distribution of patients among various laparoscopic procedures in both the groups. (Table 1) The mean operating time was 127.5 ± 34.83 minutes in Group B and 129.3 ± 30.06 minutes in Group BD and were comparable. (Table 1).

The mean heart rate in immediate post operative period was comparable in both the groups. But thereafter, patients in group BD had lower heart rate throughout the study period as compared to group B and was significant. There was no significant difference in systolic and diastolic blood pressure both within the groups and between the groups throughout the study period (Table 2).

Table 1: Demographic Variables and Duration of Analgesia

Variables		Group B	Group BD	p Value
Age Group*	≤ 30 years	10 (33.33%)	12 (40%)	0.59
	31-50 years	14 (46.67%)	15 (50%)	0.8
	> 50 years	6 (20%)	3 (10%)	0.28
Mean Age (Years)**		38.1 ± 14.78	36.8 ± 11.42	0.697
Gender*	Male	15 (50%)	14 (46.67%)	0.8
	Female	15 (50%)	16 (53.33%)	0.8
Laparoscopic Procedure*	Appendicectomy	16 (53.33%)	13 (43.33%)	0.44
	Cholecystectomy	9 (30%)	11 (36.67%)	0.58
	Hernia Repair	2 (6.67%)	4 (13.33%)	0.39
	Hysterectomy	3 (10%)	2 (6.67%)	0.64
Duration of Surgery (Min)**		127.5 ± 34.83	129.3 ± 30.06	0.2
Duration of Analgesia (Min)**		296.17 ± 67.42	617.67 ± 105.16	0.001

* Expressed as Numbers (percentages)

** Expressed as mean ± standard deviation

Table 2: Postoperative Hemodynamic Variables

Time interval	Heart Rate** Beats/Min			Systolic Blood Pressure** mm Hg			Diastolic Blood Pressure** mm Hg		
	Group B	Group BD	p-value	Group B	Group BD	p-value	Group B	Group BD	p-value
Baseline	80.9 ± 7.73	78.2 ± 7.0	0.162	112.67 ± 7.84	111.67 ± 6.47	0.592	73.67 ± 8.08	73.33 ± 5.46	0.852
5 mins	84.87 ± 8.04	74.2 ± 6.83	0.000	116.33 ± 7.18	112 ± 7.14	0.023	78 ± 6.1	74.33 ± 5.68	0.019
15 mins	107.73 ± 7.64	100.53 ± 11.89	0.007	133 ± 7.49	130 ± 6.94	0.113	89.67 ± 9.27	89 ± 8.03	0.767
30 mins	104.07 ± 7.55	87.67 ± 11.85	0.000	127 ± 6.51	123.33 ± 6.6	0.035	83.67 ± 6.14	80 ± 6.43	0.028
45 mins	101 ± 7.34	79.93 ± 11.36	0.000	123 ± 7.49	119 ± 8.03	0.051	81 ± 4.02	78 ± 6.1	0.028
60 mins	96.97 ± 6.02	77.53 ± 10.95	0.000	119.67 ± 7.64	115.67 ± 6.78	0.036	73.67 ± 8.46	76 ± 4.98	0.489
90 mins	92.93 ± 6.11	75.97 ± 10.49	0.000	117 ± 7.94	114 ± 7.7	0.143	75.67 ± 7.73	74.33 ± 5.68	0.45
2 hrs	89.67 ± 5.45	74.17 ± 8.84	0.000	114.67 ± 7.3	112 ± 6.64	0.144	74.67 ± 5.07	74.67 ± 5.71	1.0
6 hrs	86 ± 6.63	74.17 ± 7.12	0.000	112.33 ± 8.97	113 ± 7.49	0.756	76 ± 5.63	75.33 ± 5.07	0.632
12 hrs	83.6 ± 5.5	73.43 ± 7.05	0.000	112 ± 8.46	114.67 ± 7.32	0.197	76 ± 5.63	76 ± 4.98	1.0
24 hrs	79 ± 5.91	73.5 ± 4.12	0.000	119.67 ± 7.64	117 ± 7.94	0.191	79.33 ± 7.39	77 ± 4.66	0.149

** Expressed as mean ± standard deviation

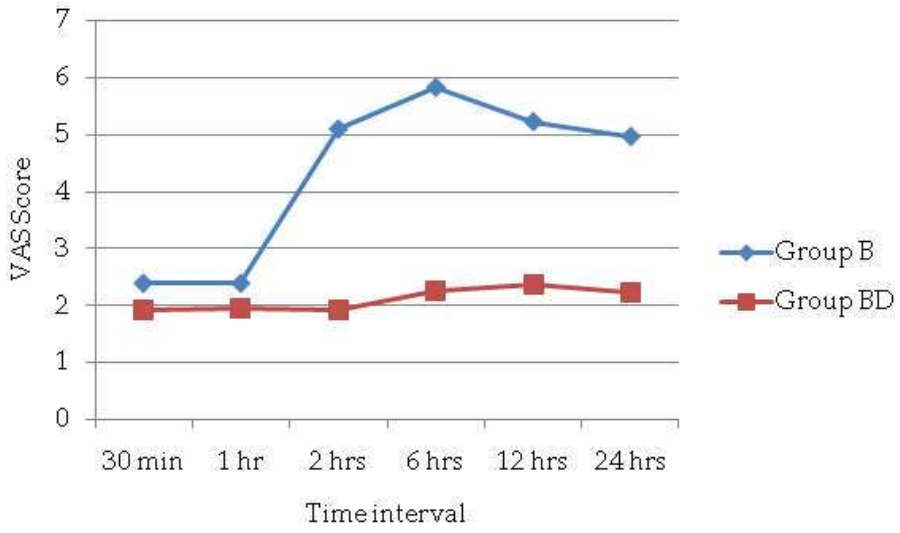
Table 3: Visual Analog Scale Score

Time Interval	Group B		Group BD		p Value
	Mean	SD*	Mean	SD*	
30 min	2.4	0.56	1.93	0.52	0.002
1 hr	2.4	0.56	1.97	0.49	0.002
2 hrs	5.1	0.99	1.93	0.52	0.000
6 hrs	5.83	0.91	2.27	1.23	0.000
12 hrs	5.23	1.07	2.37	1.03	0.000
24 hrs	4.97	0.89	2.23	0.93	0.000

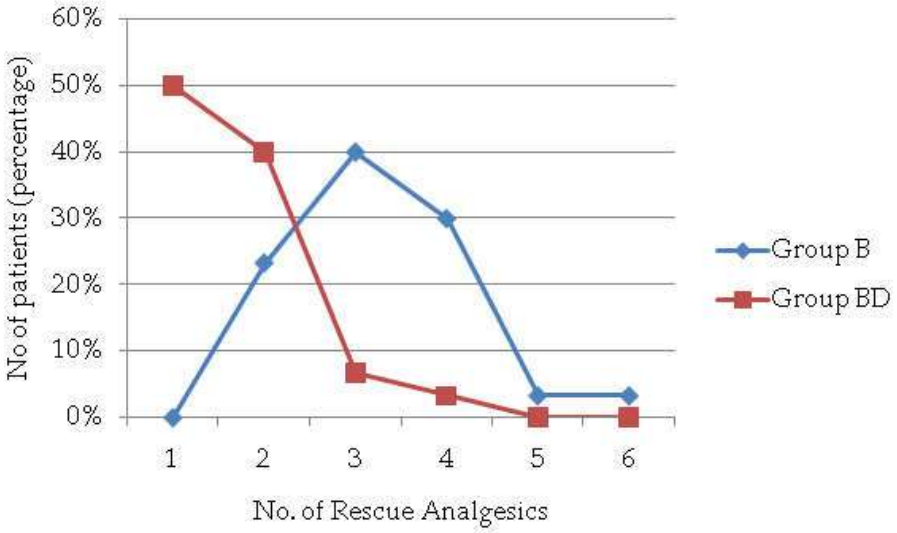
* Standard Deviation

Table 4: Complications

Complications	Group B		Group BD	
	Number	Percentage	Number	Percentage
Nausea	2	6.6%	2	6.6%
Vomiting	3	10%	2	6.6%
Shoulder Pain	0	0	0	0



Graph 1: Visual Analog Scale Score



Graph 2: Number of Rescue Analgesia

The duration of postoperative analgesia were 296.17 ± 67.42 minutes in Group B and 617.67 ± 105.67 minutes in Group BD with $p = 0.001$. Thus Group BD had significantly prolonged duration of analgesia compared to group B. (Table 1) Inter group VAS score were analyzed and variation in VAS score was found to be statistically significant $p < 0.05$. The VAS for the group with dexmedetomidine was found to be low throughout the study period compared to bupivacaine group. (Table 3, Graph 1) As a result, the number of rescue analgesia needed was comparatively low in group BD compared to group B (Graph 2).Thus highlighting that patients in group BD had adequate and prolonged duration of post-operative analgesia. There were no significant incidence of adverse effects in both the groups. The incidence of nausea and vomiting were similar in both the groups and none of the patients had shoulder pain (Table 4).

Discussion

The laparoscopy, which is considered a minimally invasive procedure, is used for various surgeries. Though the intensity of postoperative pain is far less in laparoscopic surgeries when compared to open traditional surgeries, effective analgesic treatment after laparoscopic surgeries still remain a clinical challenge. The patients undergoing laparoscopic surgery tend to expect a painless postoperative period because of common beliefs about this type of surgery [11]. Pain is the main reason for prolonged hospital stay and also the primary reason for prolonged convalescence. So, it is an essential task to provide adequate postoperative analgesia.

The abdominal pain following laparoscopic surgeries is multifactorial with pain arising from the site of dissection, stretching of parietal peritoneum from intraperitoneal gas insufflation, Carbon dioxide (CO_2) retention, prolonged elevation of diaphragm, release of inflammatory mediators of pain and irritation produced by blood. The CO_2 dissolution, intra-abdominal acidosis, and the consequent peritoneal irritation and possible phrenic nerve damage may occur for a longer period, if the gas is not evacuated completely at the end of the procedure. Residual gas also may result in a loss of peritoneal surface tension and support to the abdominal viscera, thus contributing to postoperative pain [12]. The shoulder pain secondary to diaphragmatic irritation, is a frequent postoperative observation following laparoscopic procedures [13]. It is considered to be the result of stretching of diaphragm by the pneumoperitoneum, leading to neuropraxia of the phrenic nerve and local inflammatory stimuli such as ischemia, compression and chemical irritation stimulating the sub diaphragmatic fibers [14].

There is marked inter individual variation in pain following laparoscopy and the reason remains unclear. But could be due to multiple factors including duration of surgery, the degree of invasiveness of the procedure, the experience of surgeon and the amount of peri-operative bleeding. It could also be influenced by the size of the trocars and the use of suction to remove any blood.

Various analgesics (opioids and non-opioids) via different routes, for example oral, intravenous, neuraxial blockade and intraperitoneal instillation can be used to alleviate postoperative pain. In addition, growing evidence suggests that the treatment should be multimodal and opioid sparing, to accelerate recovery and avoid potential side effects. The rationale for intraperitoneal administration of drugs for the treatment of the pain following laparoscopic surgery is that the trauma to anterior abdominal wall and visceral organs causes visceral component of the pain and residual insufflated gas causes shoulder pain due to irritation of phrenic nerve. Intraperitoneal local anaesthetic is likely to block the free afferent nerve endings in the peritoneum. Systemic absorption of local anaesthetic from the peritoneal cavity may also play a part in reduced nociception. This decrease in postoperative pain following intraperitoneal instillation of local anesthetics had been observed among patients undergoing herniorrhaphy and gynecological procedures [15,16]. Bupivacaine is one such local anesthetic that is long acting and has wide margin of safety [4].

The analgesic effects of Dexmedetomidine, a highly selective α_2 adrenergic agonist are complex. Dexmedetomidine appears to exert analgesic effects at the spinal cord level and at supraspinal sites by modulating the release of substance P. It may also provide antinociception through nonspinal mechanisms like activation of α_{2A} receptors, inhibition of the conduction of nerve signals through c and aδ fibers and the local release of encephalin [10,17,18].

Not many studies are available in literature, assessing the efficacy of the intraperitoneal instillation of local anaesthetic solutions with dexmedetomidine for postoperative pain relief following laparoscopic surgeries.

Hence this prospective, randomized study was carried out to compare the efficacy of intraperitoneal instillation of dexmedetomidine with bupivacaine with that of bupivacaine alone on postoperative pain relief in patients undergoing laparoscopic surgeries. In the present study, the primary objective was to assess the duration of analgesia i.e, the time between intraperitoneal instillation of drug to the first demand of analgesia and to compare the intensity of postoperative pain using VAS score up to 24 hours. The secondary objective was to assess the analgesic request rate in initial 24 hours postoperatively.

The demographic variables were comparable between both the groups. There was no significant difference in the distribution of patients among various laparoscopic procedures in both the groups. The duration of surgery, which by itself is an independant risk factor for post-operative pain, were similar. The mean duration of analgesia was 296.17 ± 67.42 minutes in Group B and 617.67 ± 105.67 minutes in Group BD with $p = 0.001$. Thus, there was a statistically significant prolongation of postoperative analgesia when dexmedetomidine was added to bupivacaine.

This similar observation was made by Oza et al. [19] in 2016, in their prospective study on comparison of the analgesic effect of intraperitoneal instillation of dexmedetomidine with bupivacaine (B+D) with that of bupivacaine (B) alone in one hundred patients undergoing laparoscopic surgeries. They had observed that the duration of analgesia was significantly prolonged and the requirement of rescue analgesic in 24 hours was significantly reduced in group B+D compared to group B. In a similar study by Shukla et al. [20] in 2016, they had observed that addition of dexmedetomidine to bupivacaine resulted in lower VAS scores and analgesic consumption in 24 hrs and longer duration of analgesia.

In our study, the patients who received dexmedetomidine as adjuvant with bupivacaine had significantly lower VAS scores throughout the postoperative period compared to patients who received bupivacaine alone. Chiruvella et al. [21] in 2016, in their study on antinociceptive effects of intraperitoneal dexmedetomidine combined with ropivacaine with that of plain ropivacaine alone in sixty patients undergoing laparoscopic hysterectomy, had observed that overall VAS scores in 24 hours was significantly lower, time to first request of analgesia was longer and total analgesic consumption was reduced in dexmedetomidine group than in plain ropivacaine group. In a similar study by Beder et al. [22] on assessing the effectiveness of addition of dexmedetomidine to levobupivacaine on postoperative analgesia after laparoscopic cholecystectomy, had concluded that postoperative VAS at different time intervals was significantly lower, time to the first demand of pain killer was longer and total pain killer consumption was lower when dexmedetomidine was added as adjuvant to local anesthetics.

It was observed that the number of rescue analgesia needed was comparatively low in our patients receiving dexmedetomedine (group BD). In a study by Fares et al. [23] on administration of dexmedetomidine/tramadol to bupivacaine in laparoscopic colorectal surgery, it had been found

that the total analgesic consumption was lowest in dexmedetomidine group. Ahmed et al. [24] in their study had compared the antinociceptive effect of dexmedetomidine or meperidine with bupivacaine to bupivacaine alone intraperitoneally after the laparoscopic gynaecological surgery and found that intraperitoneal instillation of meperidine or dexmedetomidine in combination with bupivacaine significantly decreases VAS score and decreases the total rescue analgesia requirement in the postoperative period.

In our study, there was a significant decrease in heart rate in group BD due to the effect of dexmedetomidine on heart; Our results were comparable with the study done by Bhattacharjee et al. [25] who compared the effects of dexmedetomidine on haemodynamics in patients undergoing laparoscopic cholecystectomy and by Arain et al. [26] who had studied the efficacy of dexmedetomidine and morphine for postoperative analgesia after a major surgery. The systolic and diastolic blood pressure studied at various intervals for initial 24 hours postoperatively, did not differ significantly both within the groups and between the groups. This result were similar to the observations made by Oza et al. [19] and Chiruvella et al. [21]

There were no significant difference in the incidence of complications in both the groups. Five patients (16%) in group B and four patients (13%) in group BD had nausea and vomiting. This observation is comparable to the observations made by Bhakhamees et al. [27] and Oza et al. [19] In contrast to our study, where none of the patients in both the groups had shoulder pain in the post operative period, Oza et al. had observed 12% patients of group B and 4% patients of group BD had postoperative shoulder pain.

Conclusion

The intraperitoneal instillation of Bupivacaine 0.25% along with dexmedetomidine 1 µg/kg in laparoscopic surgeries provides a longer duration of postoperative analgesia, better Visual Analog score and a lower analgesic requirements, with minimal side effects. To conclude, addition of dexmedetomidine to Bupivacaine for intraperitoneal instillation is a better and safe choice for prolonged postoperative analgesia following laparoscopic surgery. But further large scale studies are needed to validate our conclusion.

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