INTRAPERITONEAL BUPIVACAINE ALONE WITH DEXMEDETOMIDINE OR TRAMADOL FOR POSTOPERATIVE ANALGESIA FOLLOWING LAPAROSCOPIC CHOLECYSTECTOMY- A COMPARATIVE EVALUATION

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ABSTRACT

BACKGROUND

Post laparoscopic cholecystectomy patients complain more of visceral pain as a result of stretching of the intra-abdominal cavity, peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity. Intraperitoneal instillation of local anaesthetic agents has become an important method to control postoperative pain, nausea, vomiting and reduced hospital stay. The purpose of this double-blinded randomised controlled trial was to compare the analgesic efficacy of intraperitoneal instillation of local anaesthetic agents alone or in combination with opioids, ∝-2 agonists such as clonidine and dexmedetomidine to reduce postoperative pain following laparoscopic cholecystectomy.

MATERIALS AND METHODS

135 were equally divided into three, allocated to one of the groups by random allocation cards using computer generated random numbers. Group A (n= 45): Intraperitoneal bupivacaine 30 mL 0.25% + 5 mL normal saline (NS); Group B (n= 45): Intraperitoneal bupivacaine 30 mL 0.25% + tramadol 1 mg/kg (diluted in 5 mL NS); or Group C (n= 45): Intraperitoneal bupivacaine 30 mL 0.25% + dexmedetomidine 1 mcg/kg (diluted in 5 mL NS).

RESULTS

We found bupivacaine in combination with tramadol (Group B) has significantly lower VAS score at all points of time ($P < 0.001$) and overall VAS score and postoperative analgesia was statistically lower than with Group A. But bupivacaine + dexmedetomidine had even better VAS score underlying high efficacy of drug. Time to first request of analgesia in postoperative period was significantly delayed in Group C as compared to Group A ($P= 0.86$).

CONCLUSION

We conclude that intraperitoneal instillation of dexmedetomidine 1 mcg/kg in combination with bupivacaine 0.25% in elective laparoscopic cholecystectomy significantly reduces the postoperative pain and significantly reduces the analgesic requirement in postoperative period as compared to bupivacaine 0.25% alone and may be better than bupivacaine combined with tramadol.

KEYWORDS

Laparoscopy, Bupivacaine, Dexmedetomidine, Tramadol, VAS Analgesia.

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BACKGROUND

Postoperative pain management remains a major challenge after laparoscopic procedures. Effective pain control encourages early ambulation, which significantly reduces the risk of deep vein thrombosis and pulmonary emboli (PE); enhances patient's ability to take deep breaths to decrease the risk of pulmonary complications (e.g. atelectasis and pneumonia); and decreases the incidence of tachycardia and unnecessary investigations related to it.1 Postoperative pain may be transient and most of the time lasts for 24 hours and sometimes even up to 3 days. Intensity of pain is more immediately after surgery and less after 24 hours. There are certain more complications like postoperative nausea and vomiting, which are more in first 24 hours. This pain can be reduced by the use of local anaesthetics, non-steroidal anti-inflammatory drugs and other analgesics as well. Local anaesthetics can be given as epidural, intraperitoneal or as infiltration around the laparoscopic port sites before and after surgery.[2-6] Currently, the standard treatment for acute postoperative pain is the use of systemic opioids. Opioids bind to specific receptors located throughout the central nervous system and other tissues. Unfortunately, opioids are not without complications. Drowsiness, nausea, vomiting,

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ileus, urinary retention and pruritus are all side effects of opioids. These side effects can lead to longer lengths of stays and poor patient outcomes.[7,8,9] Another approach to control postoperative pain and limit postoperative opioid usage is local anaesthetic wound infiltration prior to wound closure. Several studies have applied both models and administered local anaesthetic, both prior to and at closure.[10-14]

Injecting local anaesthetics prior to surgical incision into the surgical wound has been more extensively studied. The results in this area are mixed with several studies showing significant pain reduction.[15-21] Intraperitoneal instillation of local anaesthetic agents alone or in combination with opioids, ∝-2 agonists such as clonidine and dexmedetomidine have been found to reduce postoperative pain following laparoscopic cholecystectomy.[22-25] After laparoscopic cholecystectomy, patients complain more of visceral pain as a result of stretching of the intra-abdominal cavity, peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity, whereas after open cholecystectomy the type of pain results mostly in parietal pain.[26] Postoperative abdominal pain usually occurs during the first 24 hours, while shoulder pain most commonly appears the second day after laparoscopic cholecystectomy. Intraperitoneal (IP) administration of some laparoscopic surgery. Some authors suggest that intraperitoneal instillation of drugs for pain relief is effective if used before creation of pneumoperitoneum,[27] while others conclude that intraperitoneal drug administration is effective at the end of the surgery applied through a trocar.[28]

Pain after laparoscopic surgery has a visceral component as a result of surgical handling and a somatic component due to the holes made in the abdominal wall for the trocars. Shoulder pain, which is associated with peritoneal insufflation occurs especially when shoulder holders and an exaggerated Trendelenburg position are used that frequently complicate the postoperative period after the laparoscopic surgery. Various methods have been tried to relieve postoperative pain following laparoscopic procedures. IP local anaesthetics (IPLAs) alone or in combination with non-opioid analgesics have been used to reduce postoperative pain following laparoscopy. This might reduce adverse effects of opioids and postoperative pain as well.[29,30]

Aims of the Study

The purpose of this double-blinded randomised controlled trial was to compare the analgesic efficacy of intraperitoneal instillation of local anaesthetic agents alone or in combination with opioids, ∝-2 agonists such as clonidine and dexmedetomidine to reduce postoperative pain following laparoscopic cholecystectomy in terms of time to first request of analgesia, total dose of analgesia in the first 24 hours and adverse effects.

MATERIALS AND METHODS

Design

Double-blinded randomised controlled trial.

Study Period

2 years.

Sampling

135 patients ASA class I and II admitted for laparoscopic cholecystectomy in GMC, Srinagar.

Sampling Procedure

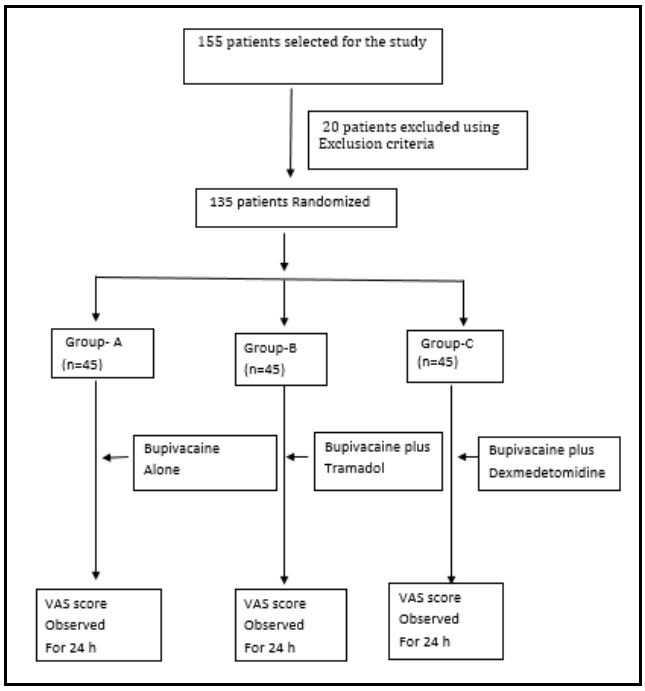
Patients were randomly allocated using random allocation cards using computer generated random numbers to one of the groups using table of randomisation, Group A (n= 45): Intraperitoneal bupivacaine 30 mL 0.25% + 5 mL normal saline (NS), Group B (n= 45): Intraperitoneal bupivacaine 30 mL 0.25% + tramadol 1 mg/kg (diluted in 5 mL NS) or Group C (n= 45): Intraperitoneal bupivacaine 30 mL 0.25% + dexmedetomidine 1 mcg/kg (diluted in 5 mL NS). Study drugs were prepared by an anaesthesiologist not involved in the study. Anaesthesiologist who observed the patient and surgeon were unaware of the drugs administered to patients of the study group until the end of the study. At the end of the surgery the test solution was given intraperitoneally before removal of trocar in Trendelenburg's position into the hepato-diaphragmatic space, on gall bladder bed and near and above hepatoduodenal ligament. The neuromuscular blockade was antagonised with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg and trachea was extubated. The nasogastric tube was removed and the patient was shifted to post anaesthesia care unit (PACU). All patients stayed in PACU for 24 hours after the end of surgery. The primary outcome variable was to compare pain (visual analogue scale [VAS]) score. The secondary outcome included time for the first request of analgesia in the postoperative period, total dose of analgesic used in 24 hours period (postoperative) and any adverse/side effects.

Justification of Sample Size

Sample size was calculated using Raosoft (http://www.rao soft.com/samplesize.html). A total sample size of 135 patients (n= 45 each for three groups) was calculated using Power and Sample size calculator (PS version 3.0.0.34), assuming 30% improvement in pain scores with error of 0.05 and power of 80%.

Statistical Method

Statistical analysis was performed using Microsoft (MS) Office Excel Software (Microsoft Excel, Redmond, Washington: Microsoft 2003, Computer software). Results were expressed as mean ± standard deviation, number and percentage (%). Data were analysed using post-hoc analysis method. Normally, distributed data were assessed using unpaired student's t-test (for comparison of parameters among groups). Comparison was carried out using Chi-square test with a P value reported at 95% confidence level. Level of significance used was P= 0.05.



Inclusion Criteria

(ASA) physical status I - II of both sexes, aged between 18 and 60 years, undergoing laparoscopic cholecystectomies were included.

Exclusion Criteria

Patients who were allergic to local anaesthetic and study drugs; patients with acute cholecystitis; patients with severe cardiac, pulmonary and neurological diseases; those in whom procedure had to be converted to open cholecystectomy; in whom abdominal drain was put were excluded from the study.

Ethical Issues

Ethical clearance was sought and obtained from the hospital ethics committee. Besides this written consent was obtained from the patients participating in the study and patient confidentiality was maintained.

RESULTS

Time	Group	Mean	P-value	Remarks
0.5	A	5.00 ± 1.60	0.021	Sig
	B	4.50 ± 0.90		
	C	3.00 ± 0.70		
1	A	5.80 ± 0.09	0.01	Sig
	B	3.50 ± 1.01		
	C	2.01 ± 0.80		
2	A	4.99 ± 1.00	0.001	Sig
	B	3.01 ± 0.90		
	C	2.00 ± 0.80		
4	A	4.45 ± 1.15	0.002	Sig
	B	2.85 ± 1.81		
	C	1.80 ± 0.22		
6	A	4.10 ± 0.85	0.011	Sig
	B	2.70 ± 1.20		
	C	2.00 ± 0.15		
12	A	5.00 ± 0.81	0.013	Sig
	B	2.50 ± 0.90		
	C	1.60 ± 0.50		
24	A	3.00 ± 0.85	0.001	Sig
	B	2.40 ± 0.80		
	C	1.05 ± 0.80		

Table 1. Postoperative VAS Score (mean ± SD) in Studied Groups

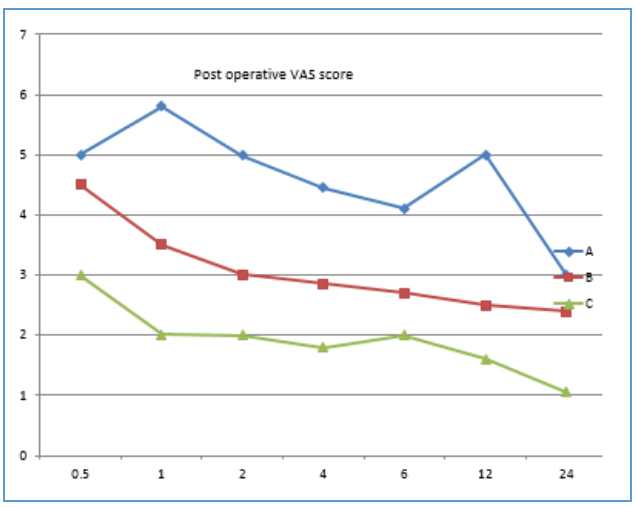


Fig. 1. Graphical Representation of Postoperative VAS Score

Group	N	Mean	SD	P-value	Remarks
A	45	4.4 ± 0.09	0.09	0.02	Sig
B	45	3.00 ± 0.46	0.46	0.01	Sig
C	45	1.78 ± 0.35	0.35	0.007	Sig

Table 2. Overall VAS over 24h Postoperatively

Furthermore, overall VAS in 24 hours was also significantly lower in Group C (1.78 ± 0.35) than Group B (3.00 ± 0.46) and Group A (4.4 ± 0.09) with a p-value of < 0.001.

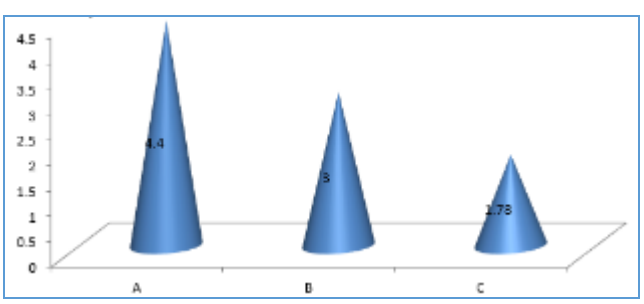


Fig. 2. Overall VAS over 24h Postoperatively

Group Comparison	P-value	Remarks
Group A vs Group B	0.005	Sig
Group A vs Group C	0.003	Sig
Group B vs Group C	0.008	Sig

Table 3. Multiple Comparison (OAVAS), Postoperatively

Above table shows the multiple comparison tests among all the study groups, which were statistically significant with p value of (0.012).

Group	N	Mean	SD	Range	P-value	Remarks
A	45	56 ± 19	3.9	37-75	0.086	Sig
B	45	119 ± 23	10.1	71-142	0.024	Sig
C	45	129 ± 21	11.4	75-150	0.045	Sig

Table 4. Time to First Request of Analgesic in Postoperative Period (min)

P= 0.004

The time to first request ranged from 37 - 75 minutes with a mean of 56 ± 19 minutes in Group A, 71 - 142 minutes with a mean of 119 ± 23 minutes in Group B and 75 - 150 minutes with a mean of 129 ± 21 minutes in Group C. The statistical difference was significant among the study groups ($p < 0.001$).

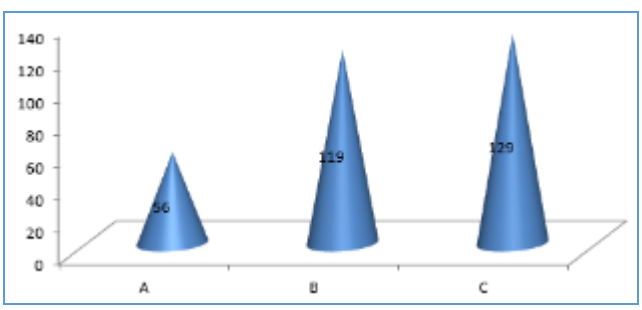


Fig. 3. Time to First Request of Analgesic in Postoperative Period

Group Comparison	P-value	Remarks
Group A vs Group B	0.005	Sig
Group A vs Group C	0.05	Sig
Group B vs Group C	0.003	Sig

Table 5. Multiple Comparisons (TTRA), Time to Rescue Analgesia

Above table shows the multiple comparison tests among all the study groups, which were statistically significant with p value of (0.049).

Group	Mean	SD	P-value	Remarks
A	170±70	3.4	0.053	Sig
B	80±30	6.9		
C	40±12	3.2		

Table 6. Total Analgesic Dose in First 24h (mg)

Total diclofenac consumption was also lowest in Group C (40 ± 12 mg) than Group B (80 ± 30) and Group A (170 ± 70).

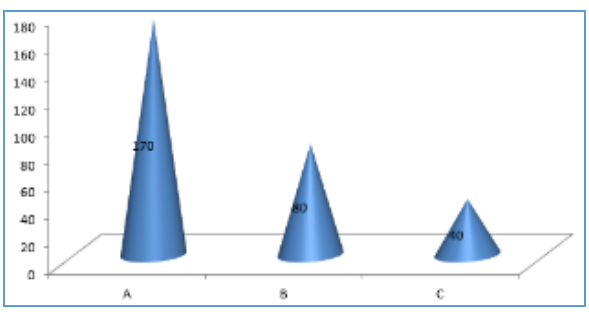


Fig. 4. Total Analgesic Dose in First 24h (mg)

Variables	Group A	Group B	Group C	P-value	Remarks
Nausea	08	06	04	0.88	Non Sig
Vomiting	04	06	0	0.66	Non Sig
Shoulder pain	28	16	05	0.90	Non Sig
Pruritus	0	2	0	0.40	Non Sig

Table 7. Postoperative Adverse/ Side Effects in Study Groups

The above table shows the postoperative adverse effects observed among the three study groups. When compared statistically, the results were found not significant with a p value of > 0.05.

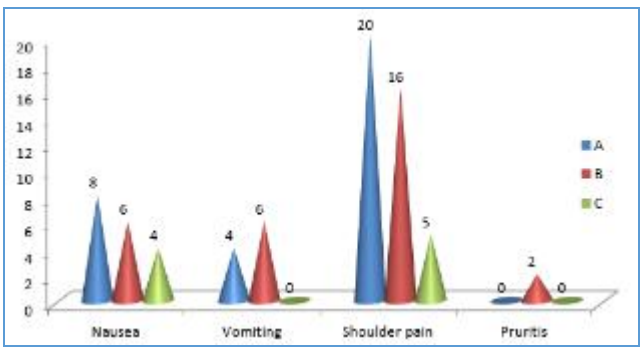


Fig. 5. Postoperative Adverse/ Side Effects

DISCUSSION

Laparoscopic cholecystectomy results in less postoperative pain as compared with open cholecystectomy and pain may be mild or moderate or even severe for some patients. After laparoscopic cholecystectomy patients complain more of visceral pain as a result of stretching of the intra-abdominal cavity, peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity, whereas after open cholecystectomy the type of pain results mostly in parietal pain.[31] Postoperative abdominal pain usually occurs during the first 24 hours, while shoulder pain most commonly appears on the second day after laparoscopic cholecystectomy. Intraperitoneal (IP) administration of some drugs can be effective for relief of pain after laparoscopic surgery. Some authors suggest that intraperitoneal instillation of drugs for pain relief is effective if used before creation of pneumoperitoneum,[32] while others conclude that intraperitoneal drug administration is effective at the end of the surgery applied through a trocar.[33]

Postoperative pain after laparoscopic cholecystectomy consists of three components, visceral, parietal and referred shoulder pain distinguishable from each other in intensity, latency and duration.[34] Previous studies[35,36] suggest that predominant cause of pain is parietal, but in contrast many other studies emphasised that in early convalescent period major portion is occupied by visceral pain because as compared to small incisions and limited trauma to the abdominal wall, the surgical manipulation and tissue destruction in visceral organs is much more.[37,38,39]

Multimodal efforts like parenteral opioids, non-steroidal anti-inflammatory drugs or local wound infiltration have been done to reduce overall pain and benefit postoperative conditions of patients undergoing laparoscopic surgeries.[40-42]

Despite their efficacy with all parenteral medications, there are associated adverse effects.

In this modern era of surgery, intraperitoneal instillation of local anaesthetic agents has become an important method to control postoperative pain, nausea, vomiting and reduced hospital stay.[43,44] In laparoscopic surgeries because of gas insufflations and raised intraperitoneal pressure, there is peritoneal inflammation and neuronal rupture with a linear relationship between abdominal compliance and resultant severity of postoperative pain.[45] Hence, we chose intraperitoneal route because it blocks the visceral afferent signals and modifies visceral nociception. The local anaesthetic agents provide antinociception by affecting nerve membrane associated proteins and by inhibiting the release and action of prostaglandins, which stimulates the nociceptors and cause inflammation.46 Intraperitoneal instillation of 0.25% bupivacaine provide effective analgesia, in addition to this we added either dexmedetomidine or tramadol to compare the antinociceptive efficacy if mixed with bupivacaine.

Golubovic et al[47] assessed the analgesic effects of intraperitoneal instillation of bupivacaine and/ or tramadol in patients undergoing laparoscopic cholecystectomy and concluded that intraperitoneal instillation of bupivacaine or tramadol or combination of both are effective method for management of pain after laparoscopic cholecystectomy and they significantly reduce postoperative analgesic and antiemetic medication. We found bupivacaine in combination with tramadol (Group B) has significantly lower VAS score at all points of time ($P < 0.001$) and overall VAS score and postoperative analgesia was statistically lower than with Group A. But bupivacaine + dexmedetomidine had even better VAS score underlying high efficacy of drug.

Memis et al[48] studied the effects of tramadol or clonidine added to intraperitoneal bupivacaine, on postoperative pain in total abdominal hysterectomy and found that combination of tramadol or clonidine with intraperitoneal bupivacaine to be more effective than bupivacaine alone. They found no significant difference between tramadol and clonidine groups in terms of efficacy, but we found dexmedetomidine to have significantly better efficacy than tramadol in combination with bupivacaine. The prominent effect of dexmedetomidine may be due to its higher efficacy in our study and higher efficacy of clonidine in the study by Memis et al.[48]

There are very few studies in the literature, which examined the analgesic effects of ά-2 agonists intraperitoneally.

Our results correlate with study done by Ahmed et al,[49] which has shown that intraperitoneal instillation of meperidine or dexmedetomidine in combination with bupivacaine 0.25% significantly decreases the postoperative analgesic requirements and decreased incidence of shoulder pain in patients undergoing laparoscopic gynaecological surgeries.

Time to first request of analgesia in postoperative period was significantly delayed in Group C as compared to Group A (P= 0.86). Memis et al[48] found no difference between tramadol or clonidine groups and in present study the time was significantly shorter in tramadol group than dexmedetomidine group (P= 0.45).

Dose of diclofenac required in postoperative period- we found statistically higher doses are required in Group A as compared to Group C or Group B, (P= 0.00, 0.000 respectively) which was in agreement with Memis et al and Ahmed et al,[50] but by contrast Memis et al[48] in their study found higher doses in clonidine group than tramadol group.

In our study, no statistically significant difference was found in regard to the adverse effects among the three study groups (P= 0.88). Only 5 (12.5%) patients in Group C suffered from shoulder pain as compared to 16 (40%) in Group B and 28 (70%) patients in bupivacaine alone group. Incidence of shoulder pain was also lower in dexmedetomidine group in study done by Ahmed et al.[51]

Multiple studies on the use α2-agonist with analgesic sparing effect have been documented. Dexmedetomidine has been used as an important adjuvant for decreasing analgesia requirement, sedative purpose and anaesthetic sparing effects.

Limitation of the present study is the postoperative pain, which is a subjective experience and can be difficult to quantify objectively when comparing various treatment options. In our study, the use of dexmedetomidine has shown a significant reduction in postoperative pain levels (VAS levels). As there are limited studies in the past, on supplementation of dexmedetomidine to intraperitoneal bupivacaine further studies with different doses of dexmedetomidine, timing and concentrations of local anaesthetics and routes of administration are needed to derive maximal benefit in terms of postoperative pain relief with minimal adverse effects after laparoscopic surgeries.

After getting approval from Institutional Ethical Committee, written informed consent was obtained from all the patients before surgery. One hundred and thirty five patients of (ASA) physical status I - II of both sexes, aged between 18 and 60 years, equally divided into three groups, Group A (n= 45), Group B (n= 45) and Group C (n= 45), undergoing laparoscopic cholecystectomies were included in this prospective study. Patients who were allergic to local anaesthetic and study drugs, patients with acute cholecystitis, patients with severe cardiac, pulmonary and neurological diseases, those in whom procedure had to be converted to open cholecystectomy and in whom abdominal drain was put were excluded from the study.

Patients were randomly allocated to one of the groups using table of randomisation, Group A (n= 45): Intraperitoneal bupivacaine 30 mL 0.25% + 5 mL normal saline (NS), Group B (n= 45): Intraperitoneal bupivacaine 30 mL 0.25% + tramadol 1 mg/kg (diluted in 5 mL NS) or Group C (n= 45): Intraperitoneal bupivacaine 30 mL 0.25% + dexmedetomidine 1 mcg/kg (diluted in 5 mL NS).

On arrival to operating room, an 18-gauge intravenous (IV) catheter was inserted and 6 mL/kg/h crystalloid was infused intraoperatively, monitoring of electrocardiography, non-invasive blood pressure, oxygen saturation (SpO2) was started and baseline values were recorded. Pre-oxygenation with 100% oxygen (O2) was done for 3 mins. General anaesthesia was induced with IV propofol 2.0 - 2.5 mg/kg followed by succinylcholine 2 mg/kg to facilitate orotracheal intubation. The trachea was intubated with a cuffed orotracheal tube of appropriate size and lubricated with

lidocaine jelly 2%. Anaesthesia was maintained with 60% N2O in oxygen with 0.5% - 1% isoflurane. Intermittent boluses of atracurium bromide were used to achieve muscle relaxation. Minute ventilation was adjusted to maintain normocapnia (end tidal carbon dioxide [EtCO2] between 34 and 38 mmHg) and EtCO2 was monitored. Nasogastric tube of appropriate size was inserted.

All patients stayed in PACU for 24 hours after the end of surgery. The primary outcome variable was to compare pain (visual analogue scale [VAS]) score. The secondary outcome included time for the first request of analgesia in the postoperative period, total dose of analgesic used in 24 hours period (postoperative) and any adverse/ side effects.

The intensity of postoperative pain was recorded for all the patients using VAS score at 0.5, 1, 2, 4, 6, 12 and 24 hours after surgery and overall VAS score (mean of all VAS scores). All the study patients were instructed about the use of the VAS score before induction of anaesthesia (VAS score 0- no pain, VAS score 10- worst possible pain). Patients who reported VAS 3 or > 3 were given diclofenac 75 mg intramuscularly as rescue analgesia. Patients were also observed for postoperative nausea and vomiting. Patients who suffered nausea or vomiting were given ondansetron 4 mg IV. Time to the first request of analgesia (considering the extubation as time 0), total dose of analgesia and adverse or side effects over 24 hours postoperatively were noted. There was no significant difference between the three groups regarding age, sex distribution, ASA class and duration of surgery.

There was a significant difference regarding time to rescue analgesia and the total dose of rescue analgesics required during the postoperative 24 hours in Group C (dexmedetomidine) as compared to other study groups.

There was no significant difference found regarding vital parameters (heart rate, blood pressure, respiratory rate, oxygen saturation) and adverse effects (nausea, vomiting, respiratory depression, pruritus and urinary retention) during the postoperative period up to 24 hours.

CONCLUSION

We conclude that intraperitoneal instillation of dexmedetomidine 1 mcg/kg in combination with bupivacaine 0.25% in elective laparoscopic cholecystectomy significantly reduces the postoperative pain and significantly reduces the analgesic requirement in postoperative period as compared to bupivacaine 0.25% alone and may be better than bupivacaine combined with tramadol.

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