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Efficacy of intravenous dexmedetomidine versus intraperitoneal dexmedetomidine in laparoscopic cholecystectomy – A prospective randomized double-blinded study

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ABSTRACT

Background: Dexmedetomidine now has become one of the frequently used drugs as part of a multimodal analgesic regimen to provide improved pain control at all perioperative stages for laparoscopic surgeries. **Aims and Objectives:** In this prospective, double-blind, randomized, and control trial, we compared the postoperative analgesic efficacy of intravenous (IV) dexmedetomidine and intraperitoneal (IP) dexmedetomidine in laparoscopic cholecystectomy. **Materials and Methods:** Sixty patients of the American Society of Anesthesiologists Grade I and II undergoing laparoscopic cholecystectomy were allocated into two groups. The patients in Group-IV had received 30 ml of 0.5 μg/kg Dexmedetomidine infusion intravenously plus 40 ml of Ropivacaine (30 mL of 0.5% Ropivacaine and 10 ml NS) intraperitoneally and in Group-IP received 30 ml NS intravenously and 40 ml of Ropivacaine plus Dexmedetomidine (30 mL of 0.5% Ropivacaine and 0.5 μg/kg Dexmedetomidine diluted in 10 ml NS) intraperitoneally after removal of the gallbladder. Patients were assessed during the first 24 h postoperatively for time to the first requirement of analgesia, total analgesic consumption, sedation, hemodynamics, side effects, and patient satisfaction. **Results:** Time to first request of analgesia (min) was longer (216.46 ± 42.19 vs. 108.03 ± 48.77) and total analgesic consumption (mg) was lower (92.50 ± 32.26 vs 115.0 ± 38.056) in Group-IV than in Group-IP. A significant difference was observed in visual analogue score in Group-IV at 1 h, 2 h, 4 h postoperatively and in the patient satisfaction score (P = 0.024) in comparison to Group-IP. **Conclusion:** The postoperative analgesic effects and patient satisfaction, of low dose IV Dexmedetomidine plus IP instillation of Ropivacaine, are superior to low dose IP Dexmedetomidine added to Ropivacaine.

Key words: Dexmedetomidine; Intraperitoneal instillation; Postoperative pain; Ropivacaine

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INTRODUCTION

In this new era of growing trends toward minimally invasive and minimal scar surgeries, laparoscopy has now become the gold standard technique for cholecystectomy. Although laparoscopic surgery is associated with less pain and the duration of pain is shorter than open procedures, it is not pain free in the early post-operative period. The etiology of pain after laparoscopic surgery is multifactorial including abdominal wall incision, visceral trauma, inflammation, and peritoneal irritation due to capnoperitoneum and the pain is maximum in the immediate post-operative

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period which decreases gradually.[1] Hence, the major goal of adequate post-operative pain relief is an integral part of the administration of anesthesia to be achieved by a combination of different classes of analgesic drugs along with different techniques targeting various pain mechanisms at all perioperative stages.[2]

Several approaches have been explored to reduce post-operative pain following laparoscopic surgeries. Intraperitoneal (IP) instillation of different drugs such as local anesthetic drugs alone or with adjuvants such as opioids, nonopioids, vasoconstrictors, N-methyl D-aspartate antagonists, α2 agonists, and neostigmine is a safe and effective analgesic approach used to control pain after laparoscopic surgery.[3,4] The IP route of administration of local anesthetic (IPLA) is simple and causes blockade of free afferent nerve endings in the peritoneum. The systemic absorption of local anesthetics through the peritoneal surface, which could be detected in the serum, after bolus instillation into the peritoneum, may also play a part in the analgesic effect by attenuating nociception.[5] Ropivacaine, a newer local anesthetic, with low toxicity, is currently considered the safest and long acting local anaesthetic.[6] As an IP local anesthetics, Ropivacaine has been reported to be effective in reducing pain without developing clinical toxicity.[7]

Alpha-2 agonists have both analgesic and sedative properties and lack respiratory depression. Dexmedetomidine is a potent and highly selective α2-adrenoreceptor agonist with sympatholytic, sedative, amnestic, anxiolytic, neuroprotective, and analgesic properties.[8] The peripheral analgesic effects of α2 adrenergic agonists potentiate local anesthetics mediated by binding to α2-A adrenergic receptor.[9] Now a days, Dexmedetomidine has been used frequently as an adjuvant to local anesthetics and intravenous (IV) anesthetics in various surgical procedures.

Aims and objectives

This study aims to compare the postoperative analgesic efficacy of a combination of either a low bolus dose of IV dexmedetomidine (0.5 μg/kg) with IP Ropivacaine and an IP Dexmedetomidine (0.5 μg/kg) with Ropivacaine in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

After approval of the Institutional Ethics Committee (approval no-19268/Dt-20.02.2020/IST-211/19), this prospective, double-blind, randomized, and clinical trial was conducted at a tertiary Medical center in Odisha, India, from February 2020 to December 2021. This study was registered in the Clinical Trial Registry India (CTRI/2021/05/033582).

Based on the results of the study performed by Chilkoti et al.,[10] applying the formula of sample size for comparing two means $N = \frac{(\sigma_1^2 + \sigma_2^2 / K)(Z_{1-\alpha} / 2 + Z_{1-\beta})^2}{(\mu 1 - \mu 2)^2}$, with 95% confidence interval and power of 80%, the calculated minimum sample size was 18 for each group, we included 30 patients in each group.

Sixty patients of age between 18 and 60 years, scheduled for elective laparoscopic cholecystectomy, and the American Society of Anesthesiologists Grade I and II were included in the study.

The exclusion criteria were patients with a history of allergy to local anesthetics or Dexmedetomidine, using antihypertensive drug clonidine, with BMI <18 or >30 kg/m^2, heart rate (HR) of <50/min, renal or hepatic insufficiency, bleeding disorders, and psychiatric disorders, the laparoscopic procedures converted to open cholecystectomy intraoperatively and had a bleeding liver bed for which the drains were kept.

The patients were randomized using sealed envelopes into two groups: Dexmedetomidine infusion group (Group-IV) and Dexmedetomidine IP group (Group-IP).

Group-IV

It received 0.5 μg/kg Dexmedetomidine infusion in 30 ml normal saline (NS) over 10 min intravenously plus 40 ml of Ropivacaine (30 mL of 0.5% Ropivacaine and 10 mL NS) intraperitoneally after removal of the gallbladder.

Group-IP

It received 30 mL NS over 10 min intravenously and 40 ml of Ropivacaine plus Dexmedetomidine (30 mL of 0.5% Ropivacaine and 0.5 μg/kg Dexmedetomidine diluted in 10 mL NS) intraperitoneally after removal of the gallbladder.

During pre-anesthetic checkup, the purpose and procedure of the study were explained to the patients and informed consent for anesthesia and procedure was obtained. During the pre-operative interview, detailed information regarding the visual analogue scale and communication regarding the need for rescue analgesics in the post-operative period was explained to the patients.

On the night before surgery, all patients were pre-medicated with tablet Alprazolam 0.5 mg and Ranitidine 150 mg orally and kept nil per orally for a duration of 8 h. In the operation theater, a monitor showing HR, non-invasive blood pressure, ECG, oxygen saturation, end tidal carbon dioxide ($EtCO_2$), and Bispctral index (BIS) was attached to the patient.

All the patients received premedication of inj. Glycopyrrolate 4mcg/kg iv, inj. Midazolam 0.04 mg/kg iv, inj Ondansetron 0.1 mg/kg iv and inj. Nalbuphine 0.2 mg/kg iv, 5 min before induction followed by pre-oxygenation with 100% oxygen. General anesthesia was induced with IV inj. Propofol 2 mg/kg and inj Xylocard 1.5 mg/kg. Intubation was facilitated with Inj. vecuronium 0.1 mg/kg iv. Anesthesia was maintained with a 2:1 ratio of nitrous oxide to oxygen mixture, sevoflurane 2–3%, and top-up vecuronium 0.02 mg/kg. $EtCO_2$ was maintained between 35 and 40 mmHg and BIS was maintained between 40 and 60. Laparoscopic surgery was performed by the same surgical team in similar durations. During surgery, all patients were placed in the position of the head upward 30°, right up 15°, and intra-abdominal pressure maintained at 12–14 mmHg. IP and IV drugs were prepared by an anesthesiologist not involved in the study. After removal of the gallbladder, hemostasis was achieved, the peritoneal wash was done and the patient position was changed into trendelenburg's position. Anesthesia gas mixture was discontinued, IV study solution was infused by an infusion pump over a period of 10 min and IP study solution was instilled into the hepato diaphragmatic space, on the gall bladder bed and near and above hepatoduodenal ligament through the instillation port of the laparoscope. The CO_2 was evacuated by manual compression of the abdomen and skin incision was sutured. The patient was kept in the trendelenburg position for 10 min. From the start of the study drug, HR, systolic blood pressure (SBP), diastolic blood pressure, and mean arterial pressure (MAP) were monitored at an interval of 5 min till the tracheal extubation. Neuromuscular blockade reversal was done with neostigmine 0.05mg/kg and glycopyrrolate 0.01 mg/kg iv and as per the standard extubation protocol (call for open eyes and tidal volume >5 ml/kg), tracheal extubation was performed. Extubation quality was rated using a 5-point scale:[11] (1) No coughing, (2) smooth extubation and minimal coughing (1 or 2 times), (3) moderate coughing (3 or 4 times), (4) severe coughing (5–10 times) and straining, (5) poor extubation, and (6) very uncomfortable (laryngospasm and coughing >10 times) and time to extubation was noted.

In the post-operative period, the patients were shifted to post-anesthetic care unit for observation for 24 h. Post-operative monitoring was assessed by a different anesthesiologist who was also blinded to treatment.

The primary outcome measure was the post-operative time to first request of analgesia and the secondary outcome measures were post-operative pain intensity, type of pain, total consumption of analgesia in 24 h, number of demands of rescue analgesia, level of sedation, patient's satisfaction, and post-operative adverse effects such as hypotension/hypertension, bradycardia, nausea, and vomiting.

- Time to first request of analgesia was noted, considering the time of administration of study drug as "Time 0"
- The post-operative pain intensity was assessed using visual analogue score (VAS)[12] where 0=no pain and 10=worst pain imaginable
- Level of sedation was assessed using the Ramsay sedation scale[11] (RSS) where (1) anxious and agitated or restless, or both, (2) cooperative and oriented, (3) responds to commands only, (4) brisk response to light glabellar tap or loud auditory stimulus, (5) sluggish response to light glabellar tap or loud auditory stimulus, and (6) no response
- Patient's satisfaction was assessed using the 7-point Likert scale:[13] (1) Extremely dissatisfied, (2) dissatisfied, (3) somewhat dissatisfied, (4) undecided, (5) somewhat satisfied, (6) satisfied, and (7) extremely satisfied.

HR, MAP, and SpO2 were recorded soon after shifting to the post-operative area, at an interval of 10 min till the end of the 1st h. RSS and VAS pain scores were recorded at 10 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, and 24 h. The incidence of port site pain/parietal pain (defined as superficial pain located on the abdominal wall), generalized abdominal pain/visceral pain (defined as deep, dull, more difficult to localize, and inside the abdomen) and shoulder pain was recorded. Post-operative adverse effects such as hypotension/hypertension, bradycardia, nausea, and vomiting were observed in each group. Hypotension (a decrease in SBP >25% from baseline or an SBP <90 mm Hg) was controlled by, iv inj ephedrine 6–10 mg and when the HR was <50/min, inj atropine 0.6 mg was given. Rescue analgesia inj. Diclofenac (75 mg) in 100 ml NS was considered when VAS was more than equal to 4. If patients experienced nausea or vomiting, metoclopramide 10 mg iv was given.

In Microsoft Excel, data were entered. Continuous variables were presented as means with standard deviation and categorical variables were presented as frequency and percentages. Association between two qualitative data will be done using the Chi-square test. Comparison of mean data between two groups was done using an independent t-test. $P<0.05$ was considered statistically significant. SPSS version 23 was used for statistical analysis.

RESULTS

A total of 60 patients were recruited for the study and all were completed the study without any dropout (Figure 1).

Both the groups were comparable in terms of patient characteristics and duration of surgery (Table 1).

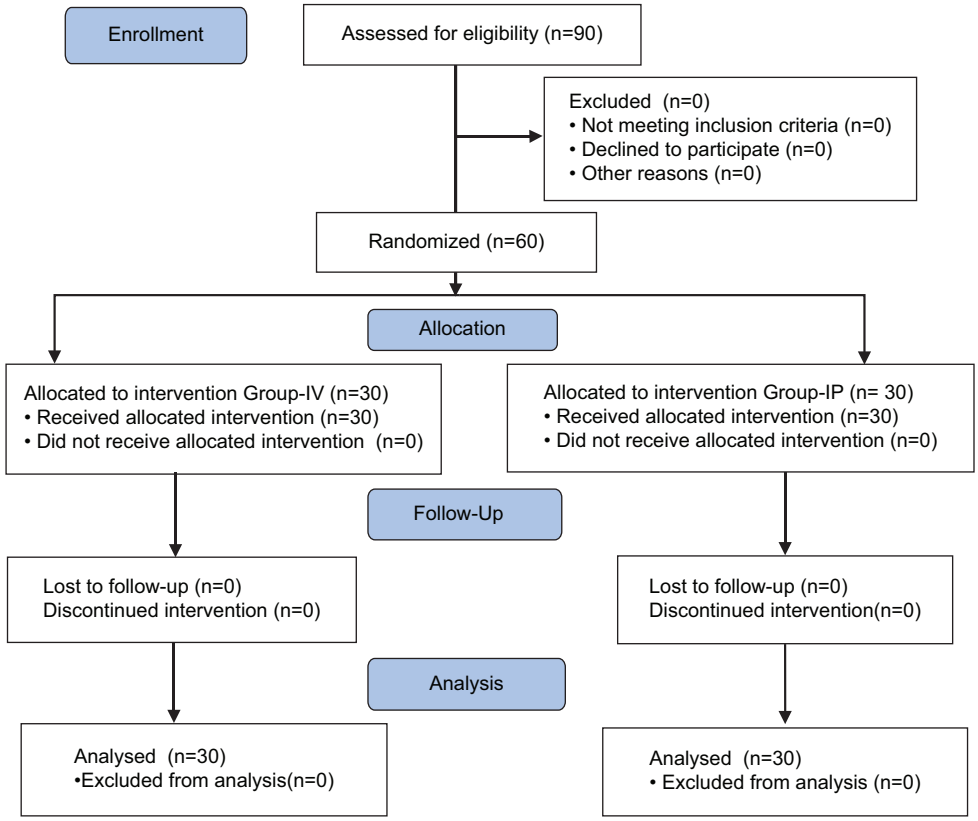

Figure 1: Consort flow diagram

Table 1: Patient characteristics, duration of surgery, and data at emergences

Variables	Group-IV (n=30)	Group-IP (n=30)	P-value
Patient characteristics			
Age (years)	45.4±13.1	42.9±12.7	0.462
Sex (M/F)	7/23	12/18	0.165
BMI (kg/m^2)	25.39±2.28	25.69±2.72	0.651
American society of anesthesiologists grading no			
Gr-1/Gr-2	20/10	25/5	0.136
Duration of surgery (min)	72.80±7.95	69.267±7.851	0.089
Data at emergences			
Time of extubation (min)	16.967±1.809	13.667±1.241	0.000*
Extubation quality. No (%)			
1	4 (13%)	0	0.000*
2	23 (76%)	8 (26%)	
3	3 (10%)	20 (66%)	
4	0	2 (6%)	
5	0	0	
Vitals at extubation			
Heart rate	75.67±9.848	81.80±11.592	0.031*
MAP	92.63±9.810	85.97±9.072	0.008*
SpO_2	98.53±0.860	98.17±0.913	0.115
Sedation score	0.60±0.675	1.13±0.507	0.0001*

Data are presented as mean±standard deviation or numbers (percentages). *P<0.05

Patients in Group-IV had a significantly longer time to first analgesia request (P=0.000), lesser requirement of total rescue analgesia in the first 24 h (P=0.016), less no of analgesic demands (P=0.017), and higher patient's satisfaction scores (P=0.024). The port site pain is also significantly less in Group-IV (26%) than in Group-IP (53%) (P=0.035) (Table 2). The mean VAS pain scores in Group-IV were comparable to Group-IP at different time intervals except at 1 h, 2 h, and 4 h, with a significant P=0.000, 0.000, and 0.008, respectively (Figure 2). The number of patients requiring analgesia was less in Group-IV compared to Group IP (Figure 3). At extubation,

Table 2: Post-operative variables

Variables	Group-IV (n=30)	Group-IP (n=30)	P-value
Time to first demand of rescue analgesia (min)	216.467 ± 42.198	108.033 ± 48.779	0.000*
Total rescue Diclofenac consumed in 24 h (mg)	92.50 ± 32.264	115.00 ± 38.056	0.016*
Number of Demand of Rescue Analgesia No (%)			
0	0	0	0.017*
1	23 (76.66%)	14 (46.66%)	
2	7 (23.33%)	16 (53.33%)	
Types of pain			
Port site pain	8 (26%)	16 (53%)	0.035*
Generalized abdominal pain	21 (70%)	22 (73%)	0.774
Shoulder pain	1 (3%)	2 (6%)	0.554
Patient Satisfaction scores. No. (%)			
5	4 (13%)	11 (36%)	0.024*
6	22 (73%)	19 (63%)	
7	4 (13%)	0	
Adverse Effects			
Nausea and vomiting	1 (3%)	2 (6%)	0.554
Hypotension	0	0	
Bradycardia	0	0	

Data are presented as mean ± standard deviation or numbers (percentages). *P<0.05

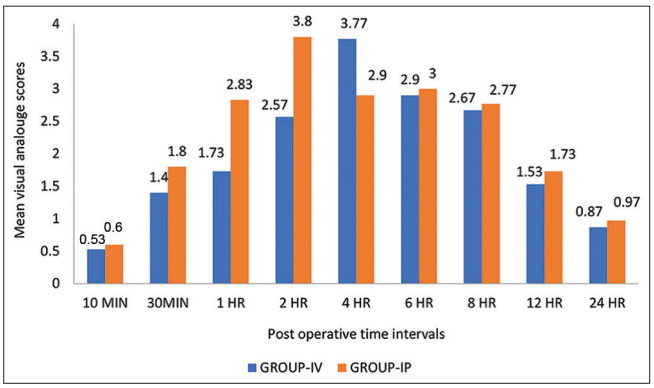

Figure 2: The mean values of visual analog scale scores for post-operative pain at different time intervals. *P<0.05

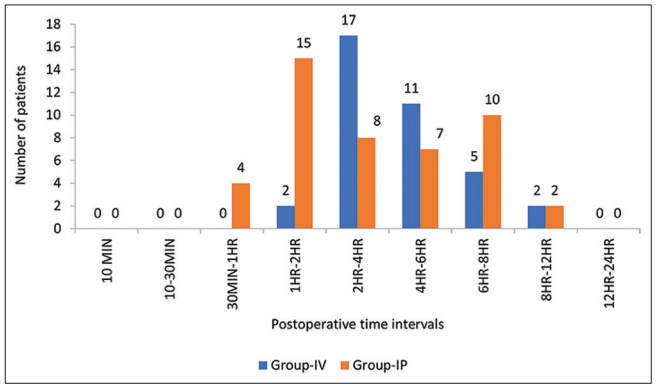

Figure 3: Number of patients requiring rescue analgesic at various time intervals. *P<0.05

a statistically significant difference was observed in HR, MAP, and RSS with P=0.031, 0.008, and 0.0001, respectively. There was a significant difference in the quality of extubation (P=0.000). The mean time to extubation was 16.967±1.809 min in Group-IV and 13.667±1.241 min in Group-IP (P-0.000) (Table 1).

The mean HR and MAP in the post-operative period at various designated intervals were comparable between the two groups, except at 10 min with a significant P=0.000 and 0.002, respectively. SpO2 at different time intervals was comparable in both groups. RSSs were significantly higher in Group-IV at 10 min and 30 min postoperatively (P=0.000 and 0.001, respectively) in comparison to Group-IP (Figure 4).

Nausea and vomiting were seen in 3% in Group-IV and in 6% in Group-IP (P=0.554). No cases of hypotension, hypoxia, bradycardia, or signs of local anesthetic toxicity were observed in both groups.

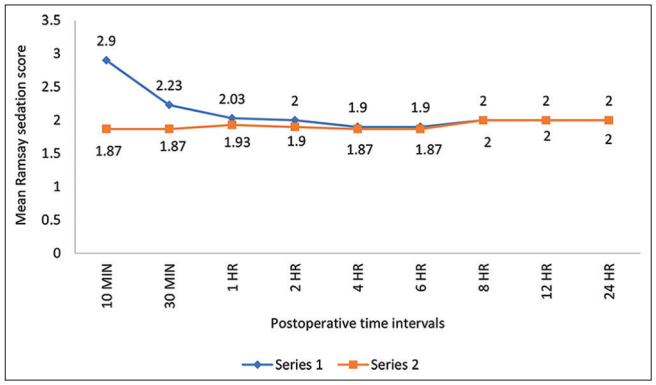

Figure 4: The mean values of Ramsay sedation scores at different time intervals. *P<0.05

DISCUSSION

This study demonstrates that IV Dexmedetomidine (0.5μg/kg) plus IP Ropivacaine during the initial 24 h after laparoscopic cholecystectomy was effective in minimizing analgesic consumption, maximizing the analgesic effect

and improving patient satisfaction without any clinically relevant hypotension, bradycardia, or oversedation.

Post-operative pain in laparoscopic cholecystectomy is multifactorial, therefore, to reduce it, multimodal treatments are suggested. Recently, multimodal analgesia is recommended because it is more effective. Dexmedetomidine is an α_2-agonist, which finds a wider area of utilization in the multimodal treatment of post-operative pain.[8,14]

The anti-nociceptive action of Dexmedetomidine has been extensively studied in laparoscopic cholecystectomy. Most studies evaluated the effect of iv Dexmedetomidine in a loading dose of 1 μg/kg bolus followed by continuous infusion of 0.5–0.7 μg/kg/h on the hemodynamic response and post-operative analgesic efficacy.[12,15,16] Few studies have evaluated the effect of iv Dexmedetomidine in a low dose of 0.2 and 0.3 μg/kg/h, respectively, on hemodynamics in patients undergoing laparoscopic cholecystectomy.[17,18]

Recently, few studies have evaluated the effect of iv dexmedetomidine in a loading dose of 0.5 μg/kg to 1 μg/kg on emergence from general anesthesia.[11,19-21] All these studies are associated with stable hemodynamics with minimal side effects but these studies did not evaluate the analgesic efficacy of dexmedetomidine. IP instillation of local anesthetic agents has become an important method for early post-operative periods to reduce pain scores and decrease the post-operative analgesic requirements after laparoscopic general surgical procedures. Several studies have evaluated dexmedetomidine as an adjuvant to IPLA in laparoscopic surgeries to improve post-operative pain scores and decrease post-operative analgesic consumption.[10,13,22]

We defined the duration of analgesia as the time period from the administration of the drug to the requirement of rescue analgesia that is a VAS score of ≥4. The mean time to first request of analgesia in this study was found significantly more in the Group-IV (216.467±42.198 min) compared to the Group-IP (108.033±48.779 min). In this study, we used Inj. Diclofenac 75 mg as rescue analgesia if VAS pain score is ≥4. The mean Diclofenac consumption in 24 h was found to be significantly reduced in the Group-IV (92.50±32.26 mg) compared to the Group-IP (115.00±38.05 mg). This is also reported by Chilkoti et al.[10] In their study, the time to first request analgesia was 210.52±161.17 min in IV vs 90.80±80.46 min in IP and mean Tramadol consumption was 137.64±52.41mg in IV vs 152.40±60.96 mg in IP.

The mean VAS pain scores in the Group-IV were significantly lower than the Group-IP at 1 h and 2 h indicating better and longer pain relief in the IV group compared to the IP group. At 4 h, the mean VAS score of Group-IV is more than Group-IP, this may be due to the combined effect of wearing off of the effect of IP anesthetics and modification of pain intensity by rescue analgesic in Group-IP. The VAS score was comparable at 10 min and 30 min indicates IP Dexmedetomidine added to Ropivacaine is effective in reducing pain immediately after operative laparoscopic cholecystectomy, similar to several studies,[7,22,23] reported that IP Ropivacaine reduces post-operative pain. The VAS score after 6 h onward was comparable in both groups. Most of the patients in Group-IV required rescue analgesia at 4–6 h, whereas in Group-IP required at 1–4 h (Figure 3). In Group-IV, only seven patients required a second dose of rescue analgesia whereas 16 patients in the Group-IP required a second dose of rescue analgesia (Table 2). Regarding the pattern of pain, it was predominantly of generalized abdominal type[1] in both the groups but the port site pain is significantly less in Group-IV (26%) than Group-IP (53%). The previous studies have demonstrated that infiltration of local anesthetics in patients' cutaneous and subcutaneous tissues after abdominal surgery reduces post-operative pain markedly.[24] It is possible that this cutaneous sensation is unaffected by IP administration of local anesthetics and less in Group-IV due to the systemic action of IV Dexmedetomidine. In this study, 22 patients were satisfied and four patients were excellently satisfied in Group-IV, whereas 11 patients were somewhat satisfied and 19 patients satisfied in Group-IP.

The effect of post-operative low dose Dexmedetomidine infusion at the end of the surgery is debatable, a few studies show a difference in time to extubation and quality of extubation[11,19] while others do not show any difference.[21] In this study, there was a significant difference in time to extubation, quality of extubation, and the hemodynamic parameters such as blood pressure and heart rate in Group-IV than the Group-IP. Our findings are consistent with other studies which proved that IV administration of Dexmedetomidine stabilizes hemodynamics and offers smooth extubation and much more easy and comfortable recovery.[11,19,20]

The sedation was more with IV Dexmedetomidine as compared to IP Dexmedetomidine at 10 min and 30 min and was statistically significantly similar to other studies.[11,19] However, the sedation score was not more than three at any time, so all patients were arousable and did not need any clinical intervention apart from routine post-operative monitoring. None of the patients in the two groups had an episode of hypotension or bradycardia. This could be attributed to the use of a low-dose of IV or IP Dexmedetomidine in this study.

The reported overall incidence of post-operative shoulder pain varies from 35 to 50% after laparoscopic cholecystectomy.[25] However, in this study, the incidence was low (3% in Group-IV and 6% in Group-IP) due to the analgesic effect of the IP drugs. Our result is similar to the study conducted by Chiruvella S et al.[22]

Limitations of the study

Limitations of the present study include that measuring the plasma levels of Ropivacaine and Dexmedetomidine after administration were not done. However, we did not exceed the maximum dose allowed[7] and no cases of toxicity were reported in the study. Second, even though double blindness was maintained, Dexmedetomidine-induced hemodynamic changes may have introduced some bias.

CONCLUSION

The use of two modalities of analgesia, IV 0.5 μg/kg Dexmedetomidine with IP Ropivacaine, was found to be associated with the lesser analgesic requirement, better analgesic effect, and better patient satisfaction compared to the use of IP administration of 0.5 μg/kg Dexmedetomidine added to Ropivacaine, without significant adverse effects in patients undergoing laparoscopic cholecystectomy. Hence, low dose IV Dexmedetomidine with IP Ropivacaine may be the preferred multimodal analgesic technique over low dose IP Dexmedetomidine added to Ropivacaine in patients undergoing laparoscopic cholecystectomy.

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SK- Concept and design of the study, prepared the first draft of manuscript, and statistical analysis **LKP-** Concept, coordination, preparation of manuscript, and revision of the manuscript, **HCD-** Interpreted the results, coordination, statistical analysis, and interpretation, **PKP-** Manuscript preparation, manuscript editing, and manuscript review, and **PS-** Interpreted the results, reviewed the literature, and manuscript preparation.

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