A Comparison of the Recovery Profile of Dexmedetomidine When Administered by Different Routes in Patients Undergoing Laparoscopic Cholecystectomy – A Randomized Controlled Trial

B. Gayathri, Gunaseelan Mirunalini*, L.N. Sundaram and R.K. Nivedita

Department of Anesthesiology, SRM Medical College Hospital And Research Center,
Potheri, SRM Nagar, Kattankulathur, Tamil Nadu, India.
*Corresponding Author E-mail:mirunalini.gunaseelan@gmail.com

Laparoscopic cholecystectomy is a minimally invasive procedure that demands a safe and fast-tracking anesthesia plan. A faster and smoother recovery of patients from anesthesia after a surgical procedure is critical for early discharge. Dexmedetomidine is a short-acting a2 agonist with analgesic, sedative, and anxiolytic properties. However, it is associated with prolonged sedation when administered through an intravenous route, thereby prolonging the recovery time from anesthesia. We conducted this study to compare the time to extubation after anesthesia when dexmedetomidine was administered through the conventional intravenous route and an interfascial transversus abdominus plane (TAP) block and rectus sheath (RS) block in patients undergoing laparoscopic cholecystectomy surgeries under general anesthesia. In addition, we also studied postoperative pain using the Visual analog scale (VAS). This study is a double-blinded, randomized controlled clinical trial conducted on 54 patients undergoing laparoscopic cholecystectomy. Patients were allocated to two groups. Group C received 50 micrograms of dexmedetomidine intravenously. Patients in group T received 50 micrograms of dexmedetomidine as an adjuvant to the 0.3% ropivacaine administered through the TAP block and RS block. The mean time for extubation in group C was 10.87 ± 1.71 minutes, and in group T was 4.37 ± 0.25 minutes, which was significant (p < 0.05, 95% CI - 5.83 to 7.17). In addition, the median postoperative VAS in group T was significantly lower at six hours, 12 hours, and 18 hours postoperatively. Hence, we conclude that dexmedetomidine, administered in the interfascial plane for laparoscopic cholecystectomy surgery, provides a better recovery profile from general anesthesia and good postoperative pain relief.

Keywords: Airway Extubation; Cholecystectomy; Dexmedetomidine; General Anesthesia; Postoperative Pain; Ropivacaine.

Laparoscopic cholecystectomy was introduced to the medical world in October 1989.[1] Decades after its introduction, the demand for this minimally invasive procedure is still on a constant rise, and so is the demand for a safe and fast-tracking anesthesia plan. A faster and smoother recovery of patients from anesthesia after a surgical procedure is critical for early discharge. Dexmedetomidine was approved for human use in 1999. It is a short-acting á2 agonist with analgesic, sedative, and anxiolytic properties[2], making it the most preferred agent of choice in surgeries

requiring minimal hospital stay like laparoscopic cholecystectomy. Dexmedetomidine is usually administered through an intravenous route. The literature library is flooded with numerous clinical studies on the recovery profile of intravenous dexmedetomidine from general anesthesia[3-7] and the postoperative pain relief properties[8-11]. Intravenous dexmedetomidine is associated with undesirable side effects like prolonged sedation after surgery and prolonged extubation time from anesthesia.[6] We conducted this study to compare the extubation time from anesthesia when dexmedetomidine was administered through the conventional intravenous route and when it was administered through an interfascial transversus abdominus plane (TAP) block and rectus sheath (RS) block in patients undergoing laparoscopic cholecystectomy surgeries under general anesthesia.

In this randomized controlled trial, we proposed a null hypothesis stating that there would be no significant difference in extubation time from anesthesia between the intervention arm which received dexmedetomidine in TAP block with RS block, and the control arm, which received intravenous dexmedetomidine.

The main objective of this study was to analyze the time taken to extubation. The secondary objectives studied were the VAS score for postoperative pain at rest. Other parameters measured were a) Time taken to open the eyes after stopping sevoflurane, b) Intraoperative and postoperative Hemodynamics, c) Modified Aldrete score (MAS) at extubation, d) Time taken to attain MAS of ten, and e) Complications associated with dexmedetomidine administration.

METHODS

We included 54 patients aged 18 to 60 years old in this study. Patients belonging to ASA physical status I and II who were posted for laparoscopic cholecystectomy were included in the study. Patients with heart rate (HR) below 50/min, systolic pressure <100 mm hg, known cardiac, renal, or hepatic dysfunction, and known allergy to á2 agonists were excluded from the study. The institutional ethical committee approved the study (1891/IEC/2019), and informed written consent was obtained from all the participants. The study was registered in the Clinical Trials Registry - India (CTRI/2021/04/032752).

Study design and sample size estimation

This study was designed as a randomized controlled trial with a parallel-arm design and a 1:1 allocation ratio done in a tertiary care hospital from April 2021 till the sample size was achieved. It is a double-blinded clinical study.

The sample size for each group was calculated using the formula [(Z1-á/2 + Z1-â)2 ó2(1+1/k)] / (d- Ä)2 for a superiority trial with continuous outcomes. The power of the study was 90%, and the two-sided confidence interval was 95%. The sample size required for each group of the parallel arm was 24, and the total sample size for the study was 48. The study was done on 54 patients adjusting for 10% anticipated dropout.

Statistical analysis

We used the Kolmogorov-Smirnov test to analyze the normal distribution of the collected data. Graphpad Prism was used to perform the statistical analysis. We used mean and standard deviation to express the continuous variables and the unpaired t-test to compare the groups. The median with an interquartile range was used to express discrete data. We used the Wilcoxon Rank Sum test to compare medians. Categorical variables were reported as percentages, and Pearson's chi-square was used to determine statistical significance. Wherever the P was less than 0.05, we considered the difference between groups to be significant.

Randomization, allocation concealment, and blinding methods

The random numbers were created by someone not involved in the intervention, data collecting, or data analysis procedure. The patients were randomly assigned to Group C (control group) or T (test group). Allocation concealment was done using a sealed envelope method. This envelope was handed over to an anesthesiologist not involved in the study only on the day of surgery. After administering general anesthesia to the patients, this anesthesiologist administered dexmedetomidine as per the random allocation in the envelope. The patient was then handed over to the principal investigator, who was blinded to the randomization to monitor intraoperatively and record the required parameters till the study period.

Conduct of anesthesia

Anesthesia was administered using fentanyl 2mcg/kg, propofol 2mg/kg, and vecuronium 0.1mg/kg. Maintained using O2:N20: Sevoflurane = 1:1:1.5% and vecuronium 0.05mg/kg administered according to the neuromuscular monitor.

Immediately after intubation, patients in group C received 50 micrograms of dexmedetomidine diluted in 100ml normal saline through the intravenous route over 10 minutes. They were administered TAP block and RS block using ultrasound with 50ml of 0.3% ropivacaine local anesthetic. Patients in Group T received 100 ml of intravenous plain normal saline. They were administered TAP block and RS block using ultrasound, with 50ml of 0.3% ropivacaine local anesthetic mixed with 50 mcg of dexmedetomidine.

The block was administered by a blinded anesthesiologist experienced in performing ultrasound-guided TAP and RS blocks. After strict aseptic precautions, a linear ultrasound probe (6-13 Hz probe of GE Vivid TM) was positioned in the anterior axillary line in the subcostal region. Next, a 20G Quincke's needle was inserted in-plane under an ultrasound probe to place the needle tip between the fascial planes of the internal oblique and transverse abdominis muscles. After confirming the needle tip by test injection of one-milliliter saline, fifteen milliliters of the local anesthetic as appropriate for the group allocation was injected on each side. The successful injection was confirmed by creating a lens-shaped space between the two muscle planes. Then the same ultrasound probe was placed on one side of the umbilicus, and the rectus muscle was imaged in a transverse orientation. Next, the needle tip was placed in the fascia between the anterior and the posterior rectus sheath. Then, ten milliliters of the local anesthetic as appropriate for the group allocation were injected on each side. The successful injection was confirmed by creating a lens-shaped space between the two fasciae.

Any fall in heart rate less than 20% from baseline was treated with Inj. Atropine 0.6 mg iv, drop in systolic pressure less than 20% from baseline, was treated with Inj. Ephedrine 6mg iv increased heart rate to more than 20% from baseline and was treated with Inj. Fentanyl 1mcg/kg and a rise in the systolic pressure of more than 20% from

baseline were treated with Inj.Propofol 1mg/kg bolus. The volatile agent was switched off at the time of placing the last suture by the surgeon.

Demographic variables like age, sex, weight, and ASA status were collected. Clinical variables like heart rate and mean arterial pressure were recorded from when the patient entered the operating room (0 min) and every 15 minutes after that till four hours (240 mins). Inhalational and intravenous anesthetic drugs were administered, and their total doses used intraoperatively were recorded. The primary outcome variable recorded was the time of extubation (the time taken to remove the endotracheal tube from the time of stopping sevoflurane). The secondary outcome variable measured was the VAS score at rest after extubation and every 6 hours after that for the first 24 hours and the VAS score at movement at 18 hours after extubation. Other variables collected were the time of opening eyes (the time taken to open eyes either spontaneously or on verbal command from the time of stopping sevoflurane), time taken to achieve a modified Aldrete score of ten (calculated from the time of extubation), and Modified Aldrete scores at extubation. In addition, any complications that occurred during extubation and due to drug effects like bradycardia, hypotension, hypertension, tachycardia, and emergence agitation were recorded.

RESULTS

This randomized controlled study was conducted on 54 patients who underwent laparoscopic cholecystectomy surgery under general anesthesia. Figure 1. shows the details of participant enrollment and the study flow. As seen in table 1, the demographic characteristics and the mean quantity of intraoperative anesthetic drug consumption were comparable between the groups.

The extubation time after anesthesia and the other parameters for endpoints of recovery from anesthesia was significantly lower in group T (P 0.0001) and are shown in Table 2. The resting VAS in group C at six hours, 12 hours, and 18 hours postoperative was significantly higher than in group T at the same time points. [group C = 4(3.5-5.5), 40 (31.5-44), and 51 (48.5-57.5), respectively, vs. group T = 2(1.5-3), 17(13.5-20.5), and 25(19-29.5) respectively]. These differences had a P value of

0.0001. The movement VAS at 18 hours in group C [68(63-71)] was also significantly higher than in group T [55(47.5-61)]. Figure 2 represents the box plots of the postoperative VAS for pain.

Figure 3 and figure 4 show the variability of the mean arterial pressure (MAP) and heart rate (HR) variability. The MAP and HR in the control group were much lower than in the test group till 45 minutes after administering dexmedetomidine. This was statistically significant.

There was an 18.5% incidence of bradycardia in the control arm. No participant had bradycardia in the test arm. The incidence of emergence agitation was 11.11%, and postoperative nausea and vomiting (3.7%) in group T and no cases in group C. We did not encounter any other complications.

DISCUSSION

In our study, when dexmedetomidine was administered in the abdominal wall plane blocks the recovery endpoints from anesthesia like the time to extubation, eye-opening time after
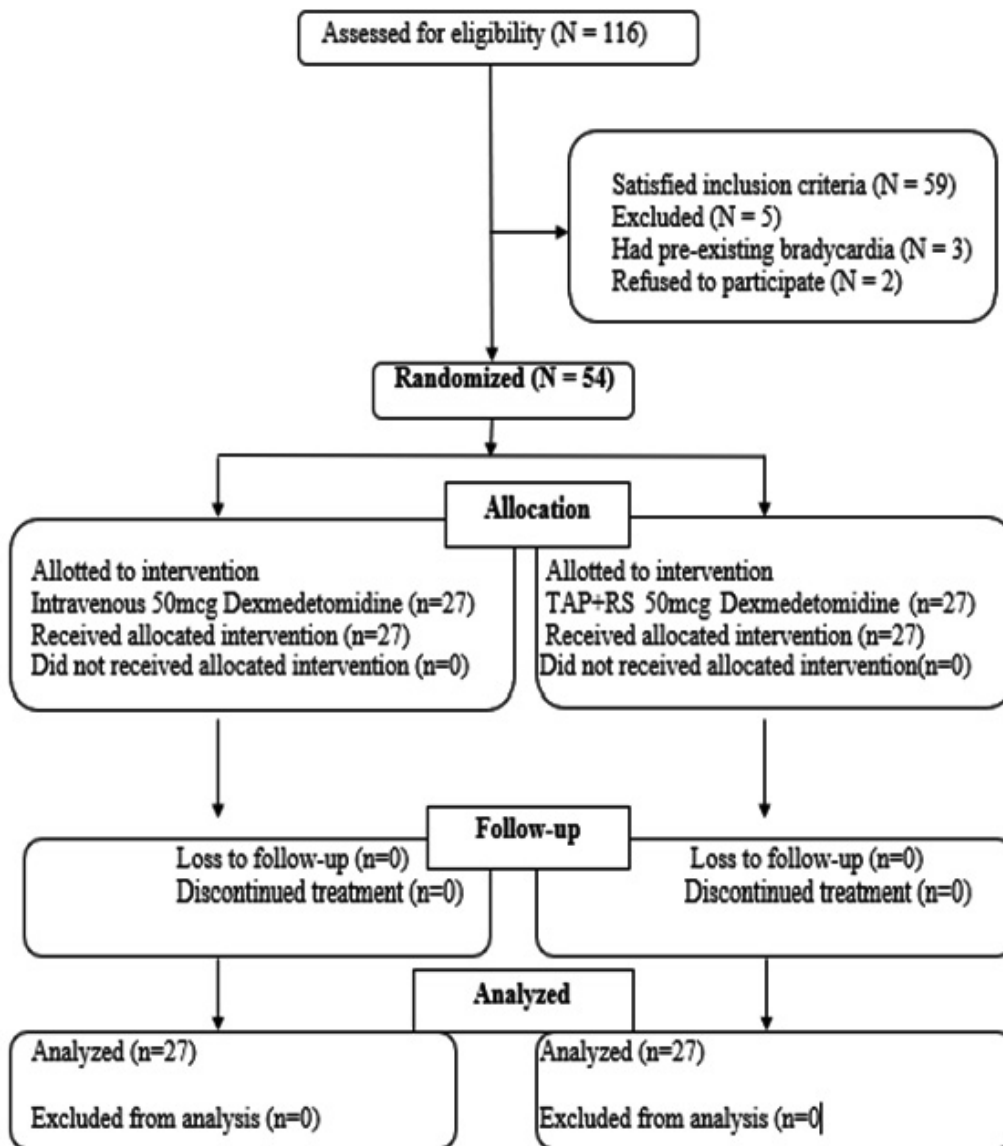

Fig. 1. Consort flow chart showing the selection process, the study flow, and data collection

Table 1. The comparison of demographic variables and the total dose of drugs used in the two groups

Variable		Group C(Mean ± SD)	Group T(Mean ± SD)	P value
Age in years		42.1 ± 7.95	43.3 ± 8.40	0.59
Gender	Male (n)	11	9	0.67
	Female (n)	16	18	
Weight in kg		59.74 ± 4.36	59.19 ± 3.83	0.62
ASA	I (n)	10	17	0.64
	II (n)	17	10	
Duration of surgery in minutes		99.74 ± 10.90	102 ± 11.98	0.47
Fentanyl in microgram		119 ± 8.29	117 ± 7.12	0.35
Propofol in milligram		116 ± 16.9	120 ± 10.6	0.30
Vecuronium in milligram		7.81 ± 0.74	7.65 ± 0.94	0.49
Sevoflurane in milliliter		15 ± 1.64	15.3 ± 1.8	0.52
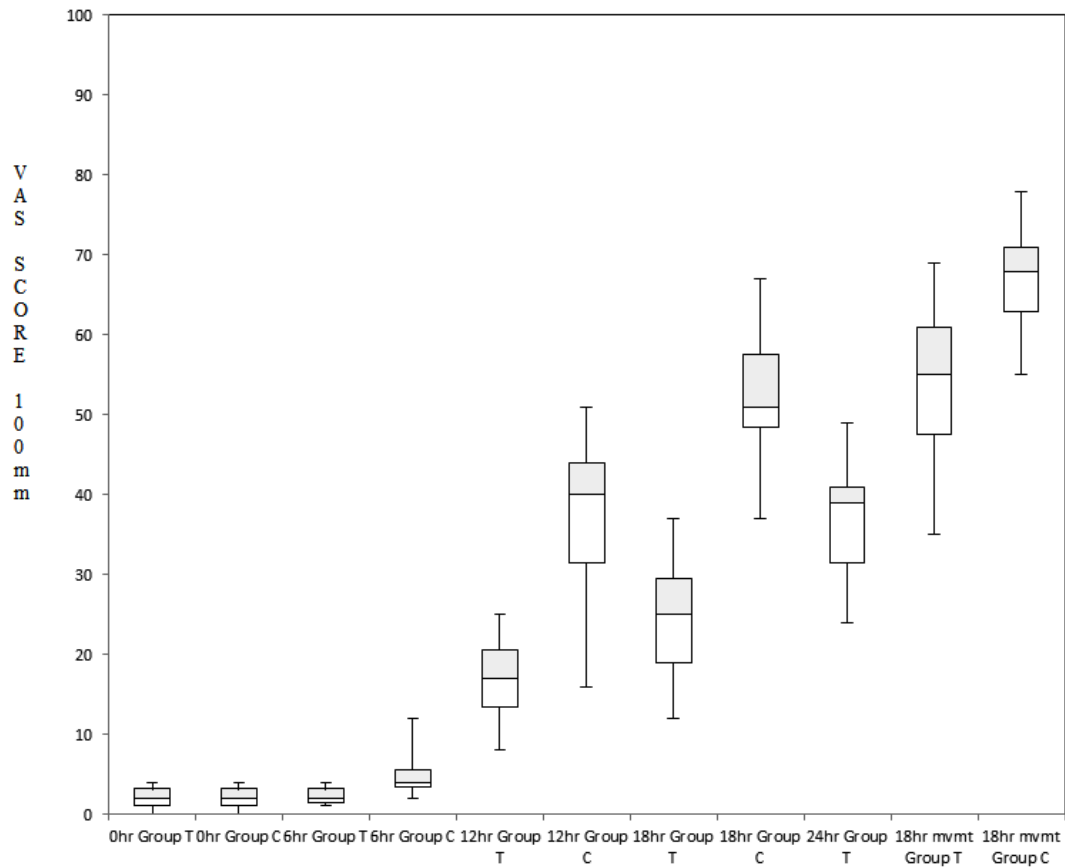
Fig. 2. Chart showing the box-whisker plots comparing median VAS scores in the post-operative period between Group C and Group T
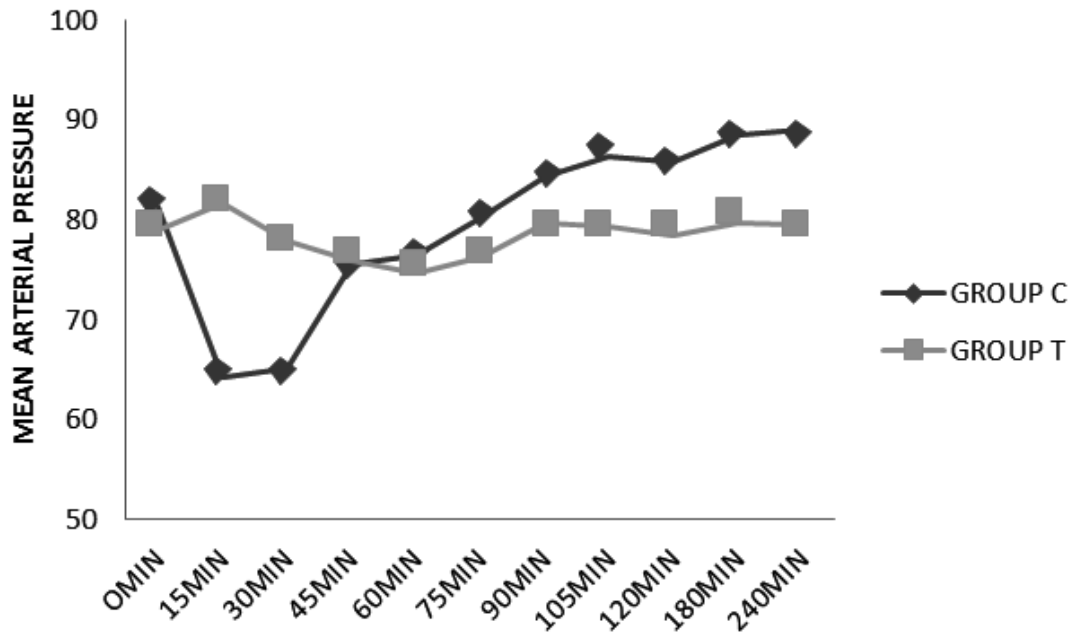
Fig. 3. Chart showing the comparison of MAP means in the intraoperative period between Group C and Group T
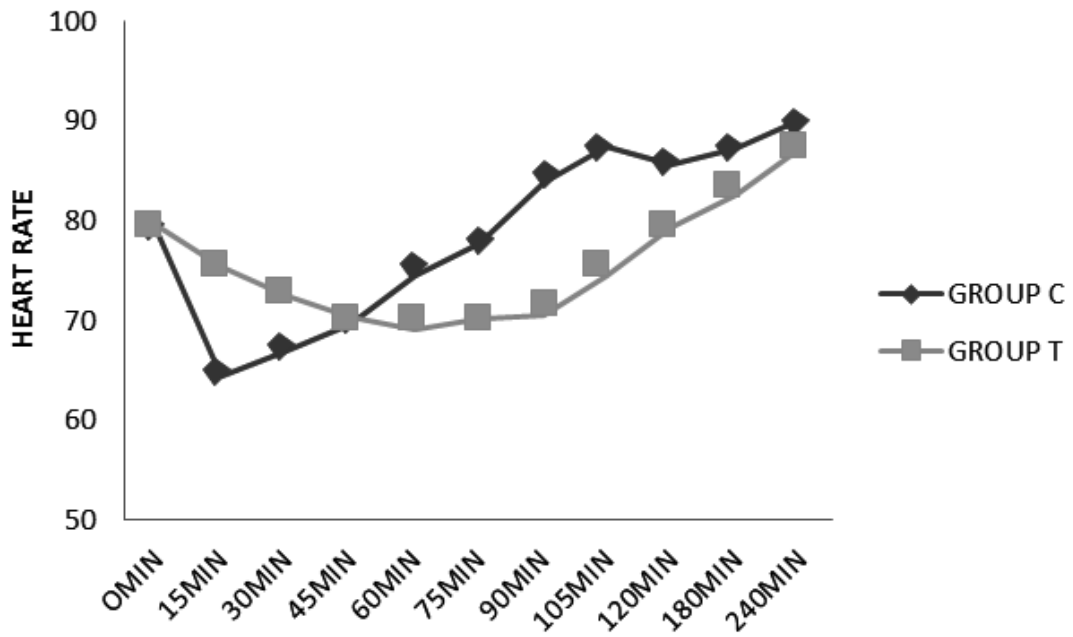

Fig. 4. Chart showing the comparison of heart rate means in the intraoperative period between Group C and Group T

Table 2. The comparison of the variables of the recovery profile between the two groups

Variable	Group C (Mean ± SD)	Group T (Mean ± SD)	P value	95% CI
Time to extubation	10.87 ± 1.71	4.37 ± 0.25	0.0001	5.83 to 7.17
Time to eye opening	8.81 ± 1.01	3.33 ± 0.22	0.0001	5.08 to 5.88
MAS at extubation *	7 (6-7)	8 (8-9)	0.0001	
Time to attain MAS 10	5.03 ± 0.6	3.37 ± 0.49	0.0001	1.36 to 1.96

* Expressed as Median (IQR)

stopping the volatile agent, and the time taken to attain a modified Aldrete score of 10 were all significantly lesser than when dexmedetomidine was administered through intravenous route. This finding is similar to a study conducted by Ye Q et al.[12] in laparoscopic cholecystectomy and also similar to studies conducted by Xue Y et al.[13] and Qin et al.[14] in laparoscopic gynecological surgeries.

Studies have concluded that the sedative effect of dexmedetomidine is through the central agonistic action on alpha 2A pre-synaptic receptors in locus ceruleus and that it is concentration-dependent.[16] This could explain the early recovery profile of patients from general anesthesia in the interfascial dexmedetomidine group, possibly due to the differences in dexmedetomidine plasma concentration.

The secondary outcome measure was postoperative pain. When dexmedetomidine was administered in the interfascial plane blocks, it significantly prolonged the duration of postoperative analgesia. Qin et al.[14] and Xue Y et al.[13] concluded in their studies that when dexmedetomidine was added to the TAP block, the patients had lower pain scores till 24 hours in the postoperative period. This correlates well with the results of our study. The analgesic action of dexmedetomidine is from both central actions on pre-synaptic alpha2A receptor agonistic action and peripheral action on inhibiting A-delta and C nerve fibers.[2,15] The analgesic effect when administered in the interfascial plan could be explained through the peripheral action mechanism mentioned previously or due to the local perineural action when co-administered with ropivacaine as suggested in a study by Keplinger et al.[16]

The hemodynamic analysis revealed that the fall in heart rate and blood pressure was immediate and more in the intravenous group. In the interfacial dexmedetomidine group, the heart rate and blood pressure were maintained steadily throughout the intraoperative and postoperative periods until four hours of observation without any drastic fluctuations. Xu L et al.[17] had administered 1mcg/kg dexmedetomidine as an adjuvant to ropivacaine in TAP and RS block in open lower abdominal surgeries and has shown that the heart rate and mean arterial pressure had a 10% fall from baseline at the time of incision. This difference in results could be attributed to the cumulative effects of other anesthetic agents used in their study. The transversus abdominis plane and rectus sheath plane are interfacial planes that contain collagenous, fibrous connective tissues and are relatively less vascular. Studies have been conducted on the systemic levels of ropivacaine administered in these planes and concluded that systemic absorption was slow.[18] This can also be assumed for the pharmacokinetics of interfascial plane dexmedetomidine, which explains the steady state of the hemodynamic response in the test arm.

The side effects we encountered in our study in the block group were agitation at emergence (11.11%) and postoperative nausea and vomiting (3.7%). This result is supported by the study conducted by Xue Y et al.[13]

The available dose regimens and pharmacokinetic models of dexmedetomidine are based on the intravenous route of administration. Interfascial plane blocks have been gaining popularity recently owing to their various advantages and patient comfort. Hence, further studies on the pharmacokinetics of dexmedetomidine in an interfascial plane are warranted for formulating precise dosing regimens. Combining dexmedetomidine with local anesthetics in the anterior abdominal wall

blocks the patients undergoing laparoscopic cholecystectomy benefits in two ways. They have a smoother and faster emergence from general anesthesia and prolonged postoperative pain relief.

This study has a few limitations. First, there is no definite method to confirm the correct administration of TAP and RS blocks except the expertise of an anesthesiologist. Hence its reproducibility by other untrained anesthesiologists to produce the same results is not guaranteed. The second limitation is that the study participants were followed only up to twenty-four hours postoperatively, as the scope of this study was to analyze the recovery endpoints from general anesthesia and postoperative pain. Hence, we have no data on the length of hospital stay, which might have been valuable to include this intervention in ERAS protocols.

CONCLUSION

When dexmedetomidine is administered through the interfascial plan for laparoscopic cholecystectomy surgery, the recovery profile from general anesthesia is improved, and postoperative pain is effectively relieved.

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