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An observational study to compare the efficacy of Intraperitoneal Ropivacaine with dexmedetomidine versus fentanyl for postoperative analgesia in patients undergoing laparoscopic cholecystectomy

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***Abstract*---**Intraperitoneal instillation of local anaesthetics with adjuvant has been used to control postoperative pain after laproscopic cholecystectomy. Aim: Compare efficacy of intraperitoneal ropivacaine with dexmedetomidine/fentanyl for postoperative analgesia in patients undergoing laparoscopic cholecystectomy. Methods: After obtaining ethical committee approval and informed consent, 62 patients aged 18-60 years, ASA I&II were divided into two groups; Group D: 18ml ropivacaine0.75% with 1µg/kg dexmedetomidine (2ml),Group F: 18ml ropivacaine0.75% with 1µg/kg fentanyl (2ml), instilled intraperitoneally after dissection of gallbladder in gallbladder fossa. Hemodynamic parameters were noted 1minute after instillation and every 15 minutes till 1hour and every hourly till 6hrs. Post-operative analgesia assessed by VAS score 1/2 hourly till 1hr and then hourly till VAS≥4 was reached. Results: Hemodynamic parameters were significantly lower in Group D upto 6hrs after instillation ($p<0.05$) and

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VAS was lower in Group D till 8hrs ($p<0.05$) post instillation as compared to group F. The duration of postoperative analgesia in Group D was 6.9±1.42 hours which was significantly longer than Group F was 3.41±0.84 hours,($p=0.001$). Conclusion: Intraperitoneal instillation of ropivacaine with dexmedetomidine is more effective for post operative analgesia than ropivacaine with fentanyl for patients undergoing laproscopic cholecystectomy.

***Keywords*---**intraperitoneal instillation, ropivacaine, dexmedetomidine, fentanyl, laparoscopic cholecystectomy.

Introduction

Laparoscopic Cholecystectomy (LC) is a frequently performed elective procedure which has many advantages over open procedures such as lesser hemorrhage, better cosmetic appearance of scars, lesser post-operative pain, and lesser recovery time, leading to shorter hospital stay and better cost effectiveness.[1,2] During laparoscopic cholecystectomy, surgeons use gas insufflation which raises the intraperitoneal pressure that results in peritoneal inflammation and neuronal rupture which leads to visceral abdominal pain that gets aggravated on coughing, deep breathing and upon movement.[3,1] It is a major hurdle for early postoperative ambulation and can cause increased risk of venous thromboembolism and respiratory complications and lengthens hospital stay.[4]

Multimodal analgesia including parenteral opioids, nonsteroidal anti-inflammatory drugs (NSAID) or local infiltration with local anesthetics are used to reduce pain.[5] Despite their efficacy, all parenteral medications have associated adverse effects.

In this advanced era of anesthesia, intraperitoneal instillation of local anesthetic drugs has become a key method to control postoperative pain, nausea, vomiting and reduced hospital stay.[6,7] Local anesthetics have the advantages that it causes less respiratory depression, reduced potential for drug abuse, less nausea, early return of bowel function and faster recovery. The local anesthetics 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. As visceral pain sensation is the major complain in patients who have undergone laparoscopic surgery, intraperitoneal instillation blocks the visceral afferent signals and modifies visceral nociception.[8]

Intraperitoneal instillation of ropivacaine provides effective analgesia and dexmedetomidine or fentanyl were added to compare their antinociceptive efficacy when mixed with ropivacaine. The antinociceptive effects of dexmedetomidine, an α2-adrenergic agonist, occur at dorsal root neuron level, where it blocks the release of substance P in the nociceptive pathway and through effect on inhibitory G protein, causes increased conductance through potassium channels leading to membrane hyperpolarization, decreasing the firing rate of excitable cells in the CNS.[9] Fentanyl produces a potent analgesic effect with rapid onset. It is potent

mu-opioid receptor agonist but has low affinity for delta and kappa opioid receptors. Its analgesic properties is 80 times more potent than morphine.[10]

Hence this study was conducted to evaluate and compare the analgesic effect of intraperitoneal ropivacaine with either dexmedetomidine or fentanyl in laproscopic cholecystectomy.

Materials and Methodology

After approval from institutional ethical committee, all the patients were explained about the purpose and nature of the study in the language they understand and written informed consent were taken. Male or female patients between age group of 18 to 60 years of ASA grade I and II posted for elective laparoscopic cholecystectomy under general anesthesia were included in the study. Patients unwilling to participate in the study, having acute cholecystitis, in whom a drain needs to be placed or laparoscopic surgeries converted to open surgeries, belonging to ASA grade III and IV, obese (BMI > 30kg/m2), having arrhythmias or heart block, psychiatric patients, pregnant & lactating women, patients taking beta blockers, with history of allergy to the study drugs or patients developing complications due to the surgical procedure were excluded from the study.

Patients were equally divided into 2 groups (Group D and Group F) of **31 patients each**. **Group D** received 18ml of ropivacaine 0.75% with 1µg/kg dexmedetomidine (diluted in 2ml normal saline) total volume 20 ml, intraperitoneally. **Group F** received 18ml ropivacaine 0.75% with 1µg/kg fentanyl (diluted in 2ml normal saline) total volume 20 ml, intraperitoneally.

Detailed pre-anaesthetic check-up of all the patients posted for elective laparoscopic cholecystectomy was done a day prior to surgery to decide the fitness and eligibility and were educated about Visual Analogue Scale (VAS) for assessment of the intensity of post-operative pain.[10] All patients were administered oral Alprazolam 0.25mg on the night before surgery and were kept nil per orally (NPO) 8 hours prior to surgery.

After arrival in operation theatre, patient was connected to multichannel monitor which records heart rate (HR), non-invasive measurements of systolic, diastolic and mean arterial pressure (SBP, DBP, MAP), continuous ECG monitoring, oxygen saturation by pulse oximeter (SpO_2) and end tidal carbon dioxide ($EtCO_2$). An 18 gauge venous cannula was secured and intravenous fluid ringer lactate was started. Patient was premedicated with Inj. glycopyrrolate 0.004mg/kg i.v., Inj. ondansetron 0.1mg/kg i.v., Inj. ranitidine 50 mg i.v and Inj. tramadol 2mg/kg i.v. Patient was pre-oxygenated with 100% oxygen for 3 minutes and induced with Inj. propofol 1-2mg/kg i.v. and Inj. succinylcholine 1.5-2mg/kg i.v. was given to facilitate intubation. Patient was intubated with cuffed endotracheal tube of appropriate size, and tube was secured after ensuring equal air entry bilaterally. Anaesthesia was maintained with oxygen: nitrous oxide at 1:1 ratio and isoflurane using circle system. Inj. atracurium loading dose 0.5mg/kg i.v. followed by maintenance with 0.1 mg/kg i.v. was administered. Patient was mechanically ventilated on volume control mode and settings were adjusted to maintain $EtCO_2$

between 35 to 45 mmHg. Intra-abdominal pressure was maintained between 12-14 mmHg. Monitoring of parameters i.e. HR, SBP, DBP, MAP, and SpO2 was noted.

After removal of the gallbladder and haemostasis, residual blood, fluid and CO_2 was thoroughly suctioned. Patients were randomly allocated into 2 groups- Group D was given 18ml ropivacaine 0.75% with 1µg/kg dexmedetomidine (diluted in 2ml normal saline) total 20 ml volume, intraperitoneally. Group F was given 18ml ropivacaine 0.75% with 1µg/kg fentanyl (diluted in 2ml normal saline) total 20 ml volume, intraperitoneally. The study solution was prepared by the consultant anesthesiologist according to the group assigned.

At the end of the surgery, before removal of the trocar, in the Trendelenberg position with right side down, the study solution was instilled intraperitoneally through the epigastric irrigation port into the hepatodiaphragmatic space, gall bladder bed and near and above the hepatoduodenal ligament. The patient was maintained in the right lowered Trendelenberg position for 10 minutes. Vitals (HR, SBP, DBP, MAP and SpO_2) were noted 1 minute after intraperitoneal instillation and every 15 minutes till one hour and thereafter every hourly till 6 hours.

Decrease in HR <50/min was considered as bradycardia and was treated with Inj. atropine 0.6mg i.v. Fall in SBP < 80 mmHg was considered as hypotension and was initially treated with 200 ml of bolus ringer lactate fluid and incremental doses of 6mg Inj. mephentermine i.v. were given if there was no improvement with fluid trial. After completion of surgery, neuromuscular blockade was reversed with Inj. neostigmine (0.05mg/kg) i.v. and Inj. glycopyrrolate (0.008mg/kg) i.v. Patient was extubated after fulfilling the extubation criteria.

Post-operative analgesia was assessed by VAS score half an hourly till one hour and then hourly till VAS ≥4 is reached and Inj. diclofenac 75 mg i.v. was given as rescue analgesia. Duration of post-operative analgesia was defined as time required for VAS to reach ≥ 4 post operatively and was noted. Post-operative complications, if arising, like nausea, vomiting, itching, respiratory depression, dryness of mouth or any other complication arising were noted.

Observation and Results

Data was collected, tabulated and analyzed. The numerical variables were presented as mean, standard deviation (SD) and categorical variables presented as percentage. The age, weight, height, gender and ASA grade distribution in both the groups were found to be comparable and no statistically significant difference was found (p>0.05) as shown in Table 1and 2.

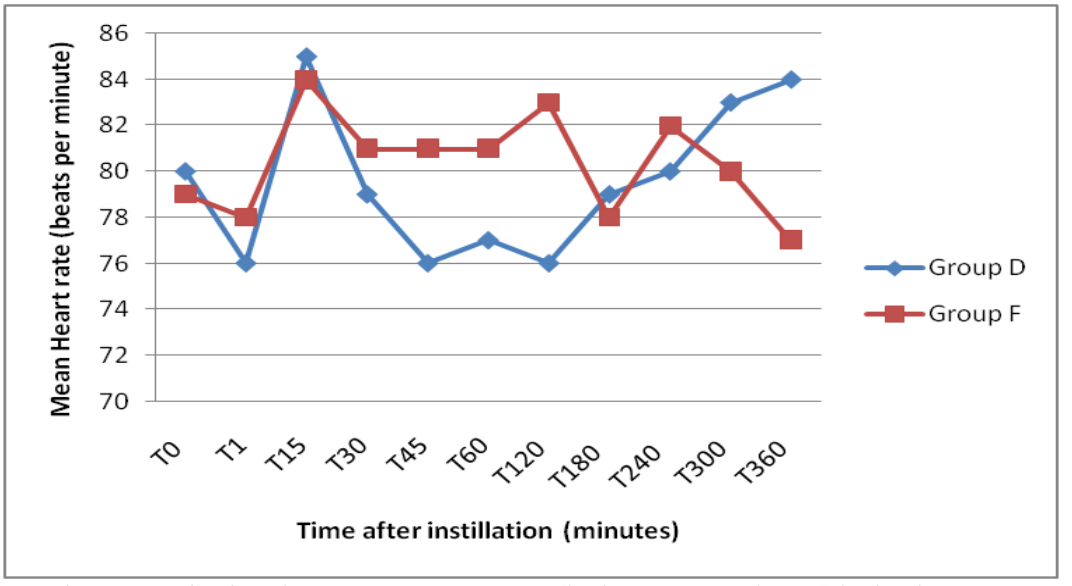
Table 1
Age, weight and height distribution in two groups

Variable	Group D (mean)	Group F (mean)	p value
Age (years)	37	37.58	0.85
Weight (kilograms)	66.871	67	0.97
Height (cm)	161.77	164.019	0.56

Table 2
Gender and ASA grade distribution in two groups

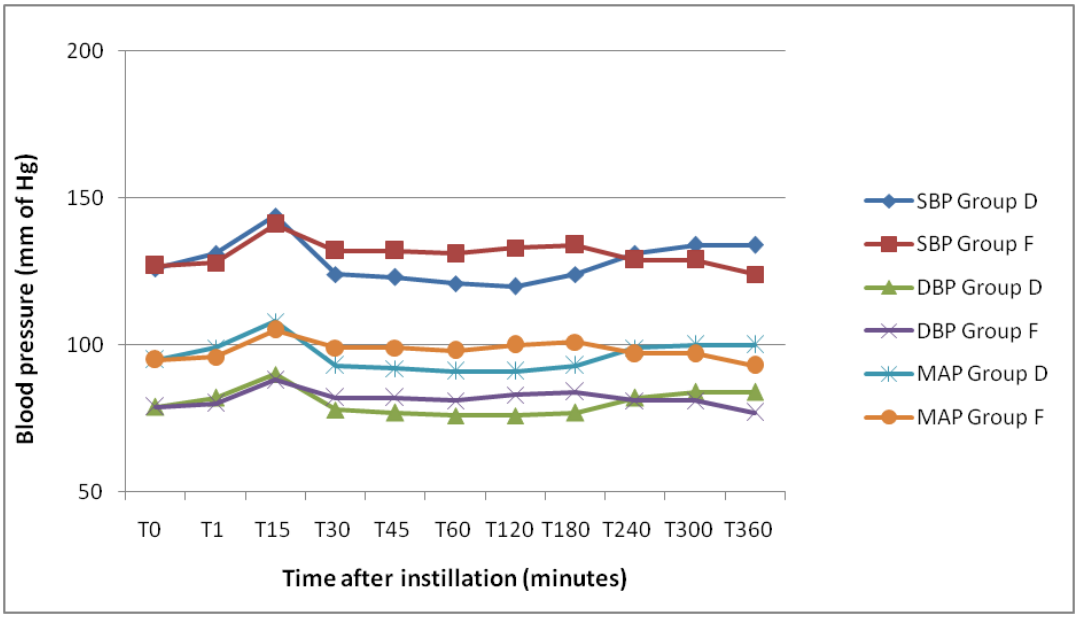
Variable	Group D (n=31)		Group F (n=31)		p value
	Number	Percentage (%)	Number	Percentage (%)	
Female	15	48.38	18	58.06	0.44
Male	16	51.62	13	41.94	
ASA grade I	18	58.06	17	54.83	0.79
ASA grade II	13	41.94	14	45.17	

The difference in mean heart rate between the two groups was statistically insignificant at the time of instillation of study drug and 1 minute after the intraperitoneal instillation of drugs ($p>0.05$). From 15 minutes to 120 minutes after the intraperitoneal instillation, the heart rate in Group D was significantly less than that in Group F ($p<0.05$). There was no significant difference in the heart rate between the two groups thereafter as shown in Graph 1.



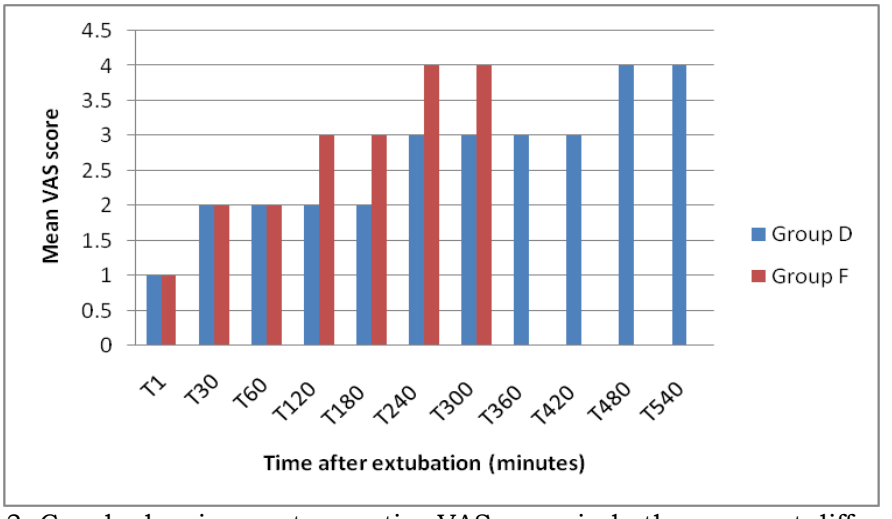
Graph 1: Graph showing Mean Heart Rate (in beats per minute) in both groups at different time intervals

The difference in mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP) and mean arterial pressure (MAP) between the two groups was statistically insignificant at the time of instillation of study drug and 1 minute after intraperitoneal instillation of study drug. From 15 minutes to 180 minutes after the intraperitoneal instillation, the mean SBP, DBP and MAP in Group D was significantly less as compared to Group F ($p<0.05$). There was no significant difference in the pressures between the groups after 180 minutes post-instillation as shown in Graph 2.



Graph 2: Graph showing mean systolic, diastolic and mean arterial pressure in both groups at different time intervals

There was no significant difference between both the groups in terms of oxygen saturation at any time interval ($p>0.05$). Mean VAS score between the two groups was not statistically significant till 60 minutes after extubation ($p<0.05$). After 60 minutes till 300 minutes after extubation, Group D had more profound analgesia with lower mean VAS score compared to Group F which was statistically significant ($p=0.0001$). After 300 minutes post-extubation, all patients in Group F reached VAS ≥ 4 while after 540 minutes post-extubation, all patients in Group D reached VAS ≥ 4 as shown in Graph 3.



Graph 3: Graph showing post operative VAS score in both groups at different time intervals

Patients of both groups were divided into two based on VAS score: mild pain (VAS 1-3) and moderate pain (VAS ≥ 4) respectively. Till 60 minutes post extubation (T60) all patients in both groups had mild pain (VAS 1-3). At 120 minutes after extubation (T120) no patients in Group D had reached VAS≥4 while 4 patients (12.9%) in Group F needed rescue analgesia (VAS 4). At 180 minutes post extubation (T180) no patients in Group D required rescue analgesia while in Group F out of 27 patients having pain, 13 patients (48.14%) had VAS 4. At 240 minutes after extubation (T240), in Group D out of 31 patients, 3 patients (9.68%) needed rescue analgesia while in Group F out 14 patients having pain, 11 patients (78.57%) needed rescue analgesia (VAS 4). At 300 minutes after extubation (T300), in Group D out of the 28 patients having pain, 2 patients (7.14%) needed rescue analgesia whileall the remaining 3 patients in Group F needed rescue analgesia (VAS 4). At 360 minutes post extubation, of the 26 patients in Group D having pain, 22 patients (84.61%) had VAS score 1-3 and 4 patients (15.38%) had reached VAS 4. All patients in Group D required rescue analgesia by 540 minutes post extubation as shown in table 3.

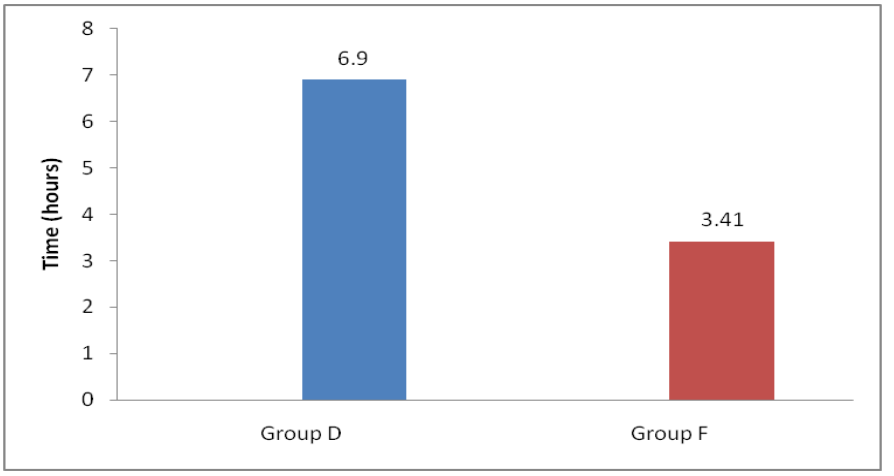
Table 3
Number of patients in both groups with respective VAS scores at different time intervals

Time	Group D			Group F		
	x_1	VAS 1-3 n(%)	VAS 4-5 n(%)	x_2	VAS 1-3 n(%)	VAS 4-5 n(%)
T1	31	31 (100)	0 (0)	31	31 (100)	0 (0)
T30	31	31 (100)	0 (0)	31	31 (100)	0 (0)
T60	31	31 (100)	0 (0)	31	31 (100)	0 (0)
T120	31	31 (100)	0 (0)	31	27 (87.1)	4 (12.9)
T180	31	31 (100)	0 (0)	27	14 (51.85)	13 (48.14)
T240	31	28 (90.3)	3 (9.68)	14	3 (21.42)	11 (78.57)
T300	28	26 (92.86)	2 (7.14)	3	-	3 (100)
T360	26	22 (84.61)	4 (15.38)	-	-	-
T420	22	12 (54.55)	10 (45.45)	-	-	-
T480	12	3 (25)	9 (75)	-	-	-
T540	3	-	3 (100)	-	-	-

x_1- total number of patients in group D having pain at a respective point of time, x_2- total number of patients in group F having pain at a respective point of time, n- number of patients, T1- 1 minute after extubation, T30- 30 minutes after extubation, T60- 60 minutes after extubation, T120- 120 minutes after extubation, T180- 180 minutes after extubation, T240- 240 minutes after extubation, T300- 300 minutes after extubation, T360- 360 minutes after extubation, T420- 420 minutes after extubation, T480- 480 minutes after extubation, T540- 540 minutes after extubation, N/A- not applicable

The duration of postoperative analgesia in Group D was 6.9±1.42 hours while that in Group F was 3.41±0.84 hours. The difference in duration of postoperative analgesia in both groups was significant (p=0.001). Group D had significantly

longer duration of postoperative analgesia as compared to Group F (p=0.001) as shown in graph 4.



Graph 4: Graph showing total duration of post operative analgesia in both groups

Three patients had episodes of nausea and vomiting in Group F but none in Group D. There was no incidence of respiratory depression, dryness of mouth, pruritus, bradycardia or hypotension noted in either group as shown in table 4.

Table 4
Incidence of side effects

Adverse Effects	Group D (n=31)	Group F (n=31)
Respiratory Depression	-	-
Dryness of mouth	-	-
Bradycardia	-	-
Hypotension	-	-
Nausea and Vomiting	-	3

Discussion

Laparoscopic cholecystectomy is currently the preferred surgical technique for cholelithiasis as it has many advantages over open procedures like better cosmetic results, lesser haemorrhage, shorter recovery time and lesser postoperative pain. Severe post operative pain increases work of breathing as it limits expansion of chest and impairs ability to cough effectively. [6]

The postoperative pain associated with laparoscopic cholecystectomy reaches a peak within first few hours following surgery but diminishes with time. It has three components: 1) Somatic pain (from incision site), 2) Visceral pain (from surgical site) and 3) Referred pain or Shoulder tip pain (due to pneumoperitoneum) [12] of which major portion of pain is visceral pain. Out of different regimens used for post operative pain such as intravenous non-steroidal anti-inflammatory drugs (NSAIDS), opioids, local infiltration, intraperitoneal

instillation of local anesthetic (IPLA), epidural analgesia, various blocks; IPLA has been chosen as effective modality. [13]

The rationale of choosing intra peritoneal route is to block visceral afferent signals and modification of visceral nociceptors which provides analgesia. Hence in our study we selected intra peritoneal instillation route for achieving post operative analgesia. Goldstein A [14] and Thierry L [15] have found that, IPLA decreases not just the visceral pain but also incidence of shoulder tip pain.

Neha Das and Charulata Deshpande in their study found that ropivacaine (0.375%) was more efficacious, longer acting with a higher intensity of postoperative analgesia than bupivacaine (0.25%). [16] Radhe Sharan et al. also had similar findings showing that ropivacaine provided better and longer acting analgesia than bupivacaine and so we selected ropivacaine as the local anesthetic in our study. [17]

Various adjutants such as clonidine, fentanyl, sufentanil, tramadol and dexmedetomidine have been used along with LA, to provide longer duration of analgesia. [18] [19] [20] [21] [22] Dexmedetomidine enhances both central and peripheral neural blockade by local anesthetic. Fentanyl produces a potent analgesic effect with rapid onset. It is potent mu-opioid receptor agonist and has higher lipophilicity compared to morphine. [10]

In our study, from 15 minutes to 120 minutes after the intraperitoneal instillation, the heart rate in Group D was significantly less than that in Group F ($p<0.05$). The SBP, DBP and MAP was significantly lower in Group D than Group F from 15 minutes to 180 minutes after instillation of study drugs ($p<0.05$). In contrast to our findings, B. Lakshmi et al. in their study comparing the antinociceptive effects of intraperitoneal ropivacaine (0.2%) with either fentanyl (1µg/kg) or dexmedetomidine (1µg/kg) in patients undergoing laparoscopic cholecystectomy observed no significant difference in the hemodynamic parameters between the study groups. [23] There is not much literature available regarding the comparative study on hemodynamic parameters after instillation of drugs intraperitoneally. Hence more studies are needed to validate these findings.
Mean VAS score between the two groups was not statistically significant till 60 minutes after extubation ($p<0.05$). After 60 minutes till 300 minutes post extubation, Group D had more profound analgesia with lower mean VAS score as compared to Group F which was statistically significant ($p=0.0001$). After 300 minutes post-extubation, 100% patients in Group F had reached VAS ≥ 4 while only 5(16.1%) patients in Group D had reached VAS≥4. We observed that the duration of post operative analgesia in Group D was 6.9±1.42 hours while that in Group F was 3.41±0.84 hours. Group D had significantly longer duration of postoperative analgesia as compared to Group F ($p=0.001$). B. Lakshmi et al found that overall VAS in 24 hours was significantly lower in the ropivacaine + dexmedetomidine group(1.68 ± 0.46) than in the ropivacaine + fentanyl group (4.47 ± 0.94) ($p<0.05$) and also observed that the time required for the first dose of rescue analgesia was longer in the ropivacaine + dexmedetomidine group (122.7 ± 24.5 min) than in ropivacaine + fentanyl group (89.3 ± 13.2 min), indicating better and longer pain relief in ropivacaine + dexmedetomidine group as compared to that of ropivacaine + fentanyl group. [23] H. Modir et al concluded that VAS

scores at different time intervals were significantly lower in the ropivacaine + dexmedetomidine group and higher in the ropivacaine group ($P < 0.001$). [10] Sunil Chiruvella et al studied the post operative pain relief provided by the intraperitoneal instillation of ropivacaine alone versus ropivacaine with dexmedetomidine in patients undergoing laproscopic hysterectomy under general anesthesia. The study concluded that VAS score at different time intervals and overall VAS in 24 hours was significantly lower in RD group than in R group. [24] Regarding adverse effects, in our study, three patients in Group F had nausea and vomiting but none in Group D. No incidences of respiratory depression, dryness of mouth, bradycardia or hypotension were noted in either group. In the study by Sunil Chiruvella, three patients in ropivacaine + dexmedetominde (RD) group and six patients in ropivacaine (R) group complained of nausea. One patient (3%) in RD group and four patients (13.3%) in R group complained of vomiting. There was no incidence of pruritus, excessive sedation, drowsiness, or dryness of mouth in both the groups. [24]

Limitation of our study is that the postoperative pain is a subjective experience and can be difficult to quantify objectively and compare when comparing treatment options. As there are very few studies in the past on addition of dexmedetomidine and fentanyl to intraperitoneal ropivacaine, further studies with different doses of dexmedetomidine and fentanyl, timing, concentrations and doses of local anesthetics are needed to provide maximal benefit in terms of postoperative pain relief with minimal adverse effects after laparoscopic surgeries.

Conclusion

Our study concluded that intraperitoneal instillation of ropivacaine(0.75%) in combination with dexmedetomidine (1µg/kg) in elective laparoscopic cholecystectomy surgery significantly reduced the postoperative pain and significantly prolonged the duration of post operative analgesia as compared to intraperitoneal instillation of ropivacaine(0.75%) with fentanyl(1µg/kg).

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