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## **A comparative evaluation of intraperitoneal instillation of 0.25% ropivacaine alone or with dexmedetomidine for postoperative analgesia following laparoscopic cholecystectomy**

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**Abstract**--Intraperitoneal instillation of local anesthetic agent with or without adjuvant in laparoscopic surgeries is a common practice now a days. This study aimed to assess the efficacy and safety of addition of dexmedetomidine (1µg/kg) to 0.25% ropivacaine by intraperitoneal instillation for postoperative analgesia in patients undergoing laparoscopic cholecystectomy. This prospective, randomized, double blind study was conducted on 80 patients of American society of Anaesthesiologists (ASA) grade I and II, either sex, aged 18 to 60 years enrolled for laparoscopic cholecystectomy to receive either Ropivacaine (0.25%) 30ml + 5 ml Normal saline (NS) in group R (n=40) or Ropivacaine (0.25%) 30ml + Dexmedetomidine (1µg/kg) + 5ml with NS in group RD (n=40) by intraperitoneal instillation, before removing trocar. All patients received infiltration of 20mL of (0.25%) ropivacaine at trocar insertion site, being 6 ml in umbilical incision, 6 ml in epigastric incision and 4 ml in both working portals after gall bladder removal. Duration of analgesia using Visual analog scale (VAS) score, total amount of rescue analgesic in 24 hrs, hemodynamic

parameters, and any adverse effects were monitored. Student t test was used to analyze the metric parameters and chi square test was used to compare the categorical variables. Duration of analgesia was significantly prolonged in group RD (746.60±93.78minutes), as compared to group R (525.89±66.64minutes) (p-value<0.0001). Total analgesic consumption within 24 hours was significantly less in Group RD (84.38±25.12mg) as compared to Group R (150.0±37.98mg) (p-value<0.0001). Demographic, hemodynamics and adverse effects profile were comparable. Intraperitoneal instillation of Ropivacaine 0.25% with Dexmedetomidine (1µg/kg) provides prolonged duration of analgesia with stable hemodynamics and minimal side effects.

**Keywords**---ropivacaine, dexmedetomidine, laparoscopic cholecystectomy.

## Introduction

Laparoscopic cholecystectomy is most accepted surgical technique for cholelithiasis with many advantages over open procedure as lesser hemorrhage, better cosmetic results, lesser post operative pain, short recovery time, leading to shorter hospital stay and less expenditure [1]. The origin of pain after laparoscopic cholecystectomy is multifactorial ,somatic Pain-from incisional site, visceral pain-from intra-abdominal trauma and referred shoulder pain- due to diaphragmatic irritation by residual CO<sub>2</sub>[2]. Postoperative pain control is amajor challenge after laparoscopic surgery as effective control of pain encourage early ambulation, so significantly reduce risk of deep vein thrombosis and pulmonary complications (enhance ability to take deep breath). Many methods have been proposed to relieve post operative pain following laparoscopic cholecystectomy [2] as intravenous NSAIDS, opioids and local infiltration. Intraperitoneal instillation of local anaesthetic alone[2] or with adjuvantsas opioids [3], alpha-2 agonists such as Dexmedetomidine[4] has been chosen as an effective modality to relieve visceral pain caused by gall bladder handling with promising results. Ropivacaine newer analgesic, with better toxicity profile compared with other local anaesthetic, such as Bupivacaine, is considered the safest, long acting local anaesthetic available in market.

Dexmedetomidine is a selective alpha 2 adrenergic against with both analgesic and sedative properties. Its use in combination with Ropivacaine is associated with prolongations of LA effect. Limited studies have been found on Dexmedetomidine (1µg/kg) as adjuvant to Ropivacaine by intraperitoneal instillation route for postoperative analgesia in patients undergoing laparoscopic cholecystectomy. So we hypothesized that Dexmedetomidine would provide prolonged postoperative analgesia with minimal adverse effects when used in dose of 1µg/kg dose as adjuvant in intraperitoneal instillation for patients undergoing laparoscopic cholecystectomy. Hence, this prospective randomized study was undertaken to assess the efficacy and safety of addition of Dexmedetomidine (1µg/kg) to 0.25% Ropivacaine by intraperitoneal instillation for postoperative duration of analgesia as primary objective and total amount of rescue analgesic

used in 24 hours, hemodynamic changes and any side effects of study drug as secondary objectives in patients undergoing laparoscopic cholecystectomy.

## Materials and Methods

After obtaining the institutional ethical committee clearance and clinical trial registration (CTRI/2019/03/017963), informed consent was taken from all the patients prior surgery. 80 patients of ASA grade I and II, either sex, aged 18 to 60 years undergoing laparoscopic cholecystectomy under General Anaesthesia were included in this prospective, randomized, double blind study conducted at our institution between August 2018 to August 2019. There were no drop outs or case failures in our study. Patients with acute cholecystitis, allergy to local anaesthetics, refusal to consent, diabetes mellitus, severe cardiac and pulmonary disease, pregnant and lactating women were excluded from study. Patients were randomly divided into two groups Group R receiving Ropivacaine (0.25%) 30ml + 5 ml NS & Group RD receiving Ropivacaine (0.25%) 30ml + Dexmedetomidine (1µg/kg) + 5ml with NS ; with 40 patients in each group using computer generated table of random number and allocation concealment was done using sequentially numbered closed opaque sealed envelope technique.

A trained anaesthesiologist, who was not involved in the study process, prepared the syringes loaded with study drug for intraperitoneal instillation and infiltration and another anaesthesiologist and surgeon who administered the drug and observed the patient were unaware of contents of loaded syringes for purpose of double blinding so both anaesthesiologist who prepared the drugs as well as observer who assessed the results were blinded. Preoperative evaluation was done according to standard protocol. On arrival to operating room, an 18 gauge intravenous (IV) catheter was inserted and multi para monitor was attached. Baseline systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, SpO<sub>2</sub> were recorded. All patients were premedicated with injection tramadol 2mg/kg and injection glycopyrrolate 0.004 mg/kg. Preoxygenation with 100% oxygen (O<sub>2</sub>) was done for 3 min. General anaesthesia was induced with injection propofol 2.0 mg/kg followed by injection succinyl choline 2 mg/kg to facilitate orotracheal intubation. Patient was intubated with a cuffed oroendotracheal tube of appropriate size.

Anaesthesia was maintained with oxygen, 1-2% sevoflurane and injection Vecuronium bromide 0.1mg/kg IV bolus and 1 mg intermittently to achieve muscle relaxation. Minute ventilation was adjusted to maintain normocapnia (end tidal carbon dioxide [EtCO<sub>2</sub>] between 34 and 38 mm Hg). Patients were placed in 15-20° reverse Trendelenberg's position with the the left side tilt position. Intraabdominal pressure was maintained at 12-14 mm Hg. After removal of gall bladder and washing peritoneal cavity with normal saline by surgeon, The study solution Group R (n=40) – received-intraperitoneal instillation of 0.25% ropivacaine 30ml + 5ml normal saline , Group RD (n=40) – received-intraperitoneal instillation of 0.25% ropivacaine 30ml + dexmedetomidine 1µg/kg making the volume 5 ml with normal saline) was given intraperitoneally before removal of trocar in 20 degree Trendelenberg's position,(kept it for 20 minutes ) equally into the hepatodiaphragmatic space, on gall bladder bed and near and above hepatoduodenal ligament. The CO<sub>2</sub> was removed carefully by

manual compression of the abdomen at the end of the procedure with open trocar.

While skin suturing all patients received infiltration of 20mL of 0.25% ropivacaine at trocars insertion site, being 6mL in the umbilical incision, 6mL in the epigastric incision and 4mL in both working portals. The neuromuscular blockade was antagonized with neostigmine (0.05 mg/kg) and glycopyrrolate (0.008mg/kg) and patients extubated. All patients stayed in Post anesthesia care unit (PACU) for 2 h after the end of surgery. The primary outcome was to compare duration of analgesia (from the time of extubation to the demand of first dose of rescue analgesic) using VAS score. The intensity of postoperative pain was recorded for all the patients using VAS score at 0, 0.5, 1, 2, 4, 6, 12, 24 h after surgery. All the study patients were instructed about the use of the VAS score before induction of anesthesia also (VAS score 0 as no pain to VAS score 10 as worst possible pain). Patients who reported VAS >4 were given injection diclofenac aqueous 75 mg Intravenous (IV) as rescue analgesia. Patients who complains of nausea or vomiting were given injection ondansetron 4 mg IV. Time to the first request of analgesia, total number of doses and amount of analgesia (mg), Hemodynamic parameters and adverse effects over 24 hours postoperatively were noted.

### Statistical analysis

A total sample size of 80 patients (n=40 each for two groups) was calculated using Power and Sample size calculator ( PS Version 3.0.0.34) with Power of 80% and 95% confidence level with  $\alpha$  error of 0.05%. Statistical analysis were carried out using SPSS software version 16.0 (SPSS Inc, Chicago, IL, USA). Microsoft Word and Excel was used to generate graphs and tables. All the numerical data were expressed as mean  $\pm$  standard deviation whereas the categorical data were expressed as numbers or frequency (%). Standard qualitative and quantitative tests was used to compare the data (e.g. paired and unpaired student-t-test, Chi-Square test). Data considered statistically significant with p-value of less than 0.05.

### Results

Table 1  
Comparison of demographic data in two groups [mean $\pm$ SD]

Basic Characteristics	Group R (n=40)	Group RD (n=40)	p-value ( >0.05 not significant)
Age in years(Mean $\pm$ SD)	40.60 $\pm$ 11.57	39.08 $\pm$ 11.63	0.55
Weight (Kg)	55.05 $\pm$ 6.26	55.60 $\pm$ 5.032	0.66
Gender(M/F)	34/6	32/8	0.58

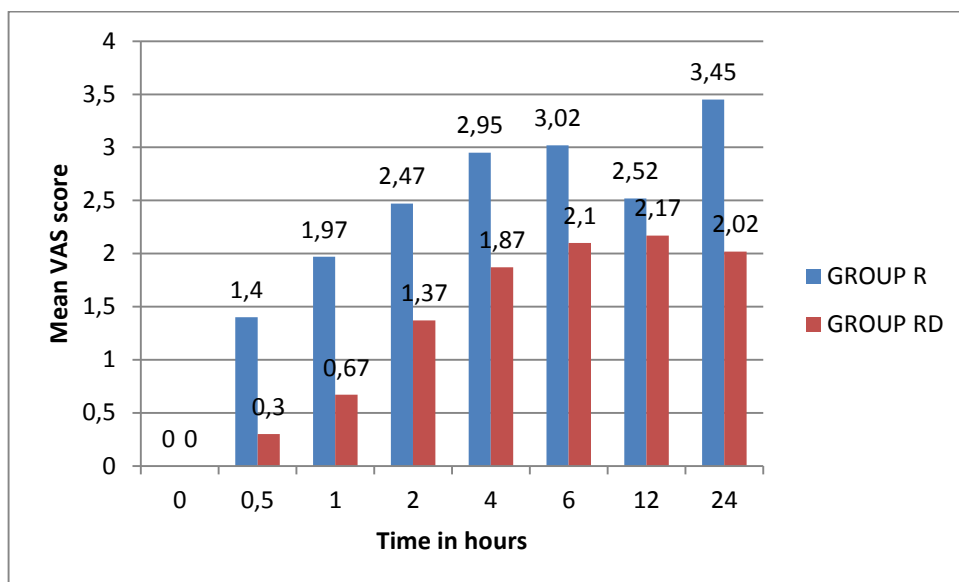


Figure 1. Comparison of post-operative mean pain score (VAS) in two groups (mean±SD)

Table 2

Comparison of mean duration of analgesia in two groups (mean±SD) (in 24 hours)

	Group R (n=40)	Group RD (n=40)	p-value
Duration of Analgesia (min)	525.80±66.64	746.60±93.78	<0.0001 Highly significant

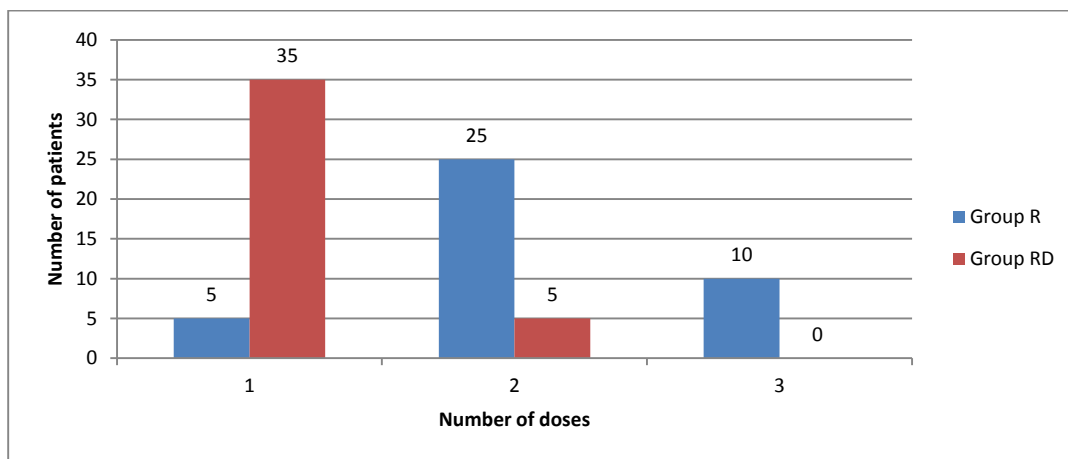


Figure 2. Comparison of no. Of doses of rescue analgesic required in two groups (in 24 hours)

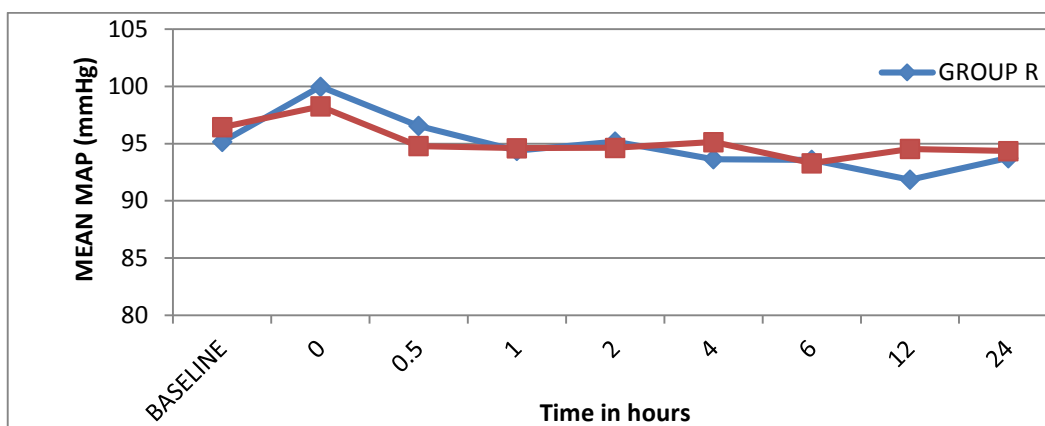


Figure 3. Comparison of Mean MAP (mm Hg) in both the groups

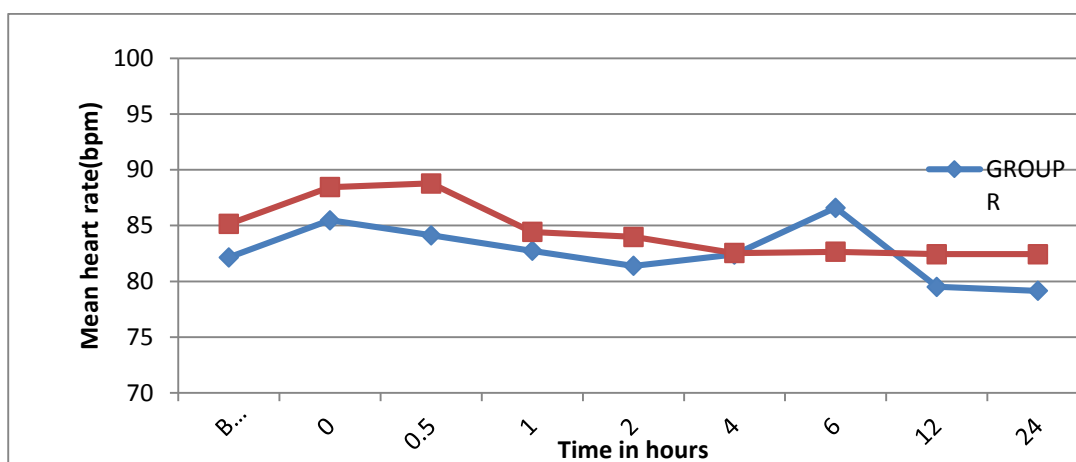


Figure 4. Comparison of post-operative mean heart rate (beat per minutes) in both the groups

Table 3

Comparison of mean of Ramsay sedation score (RSS) in both groups

Time interval (hours)	Group R (n=40) Mean±SD	Group RD (n=40) Mean±SD	p value
0 hrs	2.0±0.45	2.15±0.58	0.18
0.5 hrs	1.85±0.36	1.90±0.34	0.50
1 hrs	1.85±0.36	1.90±0.30	0.50
2 hrs	1.83±0.38	1.88±0.33	0.53
4 hrs	1.80±0.40	1.88±0.33	0.36
6 hrs	1.75±0.43	1.83±0.38	0.41
12 hrs	1.72±0.45	1.83±0.38	0.28
24 hrs	1.72±0.45	1.80±0.40	0.43

Table 4  
Comparison of adverse effects in both the groups

Variable	Group R (n=40)		Group RD (n=40)		p-value
	n	%	N	%	
PONV	3	7.5	1	2.5	0.60
Hypotension	0	0	0	0	-
Bradycardia	0	0	0	0	-
Pruritus	0	0	0	0	-
Shoulder pain	2	5.0	0	0	-

Both groups were statistically comparable (Table-I) for age, weight, sex, ASA physical status and baseline haemodynamic parameters. However both groups show female preponderance. Visual analogue scale at all-time interval was statistically significantly lower in Group RD than Group R (p-value <0.05) (Figure 1). Time to requirement of the first rescue analgesia was 525.80±66.64 minutes in group R with a range of 360 to 620 minutes as compared to 746.60±93.78 minutes with a range of 510 to 845 minutes in group RD. The difference in the mean duration of analgesia was statistically highly significant (p -value<0.0001) (Table-2). The total number of doses of rescue analgesic required were less in group RD as compared to group R (Figure-2)The mean total consumption of diclofenac in group RD was 84.38±25.12 mg while in group R was 150.0±37.98 mg which was statistically significant (p-value<0.0001). There was no significant difference in the Mean heart rate (MHR), Mean arterial pressure (MAP) (Figure-III,IV) and Mean SpO<sub>2</sub> between the two groups at any time interval postoperatively (p value>0.05). Mean of Ramsay sedation score (RSS) in intergroup analysis was found to be less than 2 at all time interval in both R and RD groups which was statistically insignificant (p-value>0.05) (Table-3). The PONV was observed in 3 patients in group R compared to 1 in group RD . There was no incidence of bradycardia, hypotension and pruritus among two groups (p value>0.05) (Table -4)

## Discussion

The present study, noted that the intraperitoneal instillation of Dexmedetomidine (1µg/kg) in combination with ropivacaine 0.25% , as compared to ropivacaine 0.25% alone , in patient undergoing laparoscopic cholecystectomy under general anesthesia , was associated with increased time to first rescue analgesia, reduced total dose of rescue analgesia in 24 hours with stable hemodynamic postoperatively. Local anesthetic(LA) Inhibits nociception by affecting nerve membrane-associated proteins and by inhibiting the release and action of prostaglandins and other agents that sensitize the nociceptors and contribute to inflammation [5].Many adjuvants like fentanyl, tramadol, α<sub>2</sub>-agonist (dexmedetomidine) have been used to enhance the analgesic effect of LA [6,7]. Dexmedetomidine is a highly lipophilic α<sub>2</sub> agonist with analgesic and sedative properties. Its central antinociceptive effect occurs at dorsal root neuron level by blocking the release of substance P in nociceptive pathway through the action of inhibitory G protein, which increases the conductance through K<sup>+</sup> channels [8,9]. IP administration of dexmedetomidine causes local analgesia by enhancement of

the hyperpolarization-activated cation channels, which prevents the nerve from returning to resting membrane potential [10]. sedative-hypnotic effect by an action on  $\alpha_2$  receptors in the locus caeruleus and an analgesic action at  $\alpha_2$  receptors within the locus caeruleus and within the spinal cord.

This study utilized 75 mg ropivacaine (0.25%) for IP instillation in one group and mixed it with dexmedetomidine ( $1\mu\text{g}/\text{kg}$ ) in another group of patients. The rationale of preferring ropivacaine was that it is a long acting agent (6-12 h), with less motor blockade and less cardiotoxicity than bupivacaine. Similar concentrations of ropivacaine were utilized by Gupta M et al 2016 [11] where intraperitoneal instillation of 0.25% Ropivacaine (50 ml, 125mg), large volumes was used in laparoscopic cholecystectomy with no toxic effects. Devalkar Priti et al 2016 [12] utilized intraperitoneal instillation of 0.25% Bupivacaine. Boody et al 2016[13] in a systemic meta analysis, stated that Ropivacaine has minimal CVS & CNS toxicity compared to Bupivacaine in same plasma concentration even in large doses of 300 mg of intraperitoneal instillation. Also this made study cost effective as 0.25% ropivacaine was used, 10 ml volume of 0.75% Ropivacaine diluted three times to prepare 0.25% ropivacaine. Nearly total blocks were administered by giving the local anesthetic agent to all regions where many surgical manipulations were applied, such as hepatoduodenal ligament, gallbladder bed, and subdiaphragmatic areas.

Dexmedetomidine enhances both central and peripheral neural blockade by local anesthetics [13]. So it was hypothesized that there would be adequate prolonged postoperative analgesia with no adverse effects as occurs with opioids as respiratory depression for patients undergoing laparoscopic cholecystectomy. In the present study,  $1\mu\text{g}/\text{kg}$  Dexmedetomidine was used, same dosage was used in studies done by Baz et al 2018[14], Shukla U et al 2015[15]. In the present study, lesser mean VAS scores were observed in group RD than group R which were statistically highly significant ( $p < 0.0001$ ) (Figure 1). The intraperitoneal instillation of dexmedetomidine in combination with ropivacaine gives better pain relief. Because of the high lipophilic nature of dexmedetomidine, it acts over the peritoneal neural receptors and blocks the nociceptive stimuli. The results are in concordance with studies conducted by Ranjita Acharya et al[16] Shukla et al[15], ahmed et al[4]. Although Shukla et al. observed the mean VAS score to be lower at all time interval but was higher as compared to this study, which could be attributed to the use of low dose of dexmedetomidine ( $0.5\mu\text{g}/\text{kg}$ ) in their study.

In the present study, the mean duration of analgesia was  $525.80 \pm 66.6$  minutes in group R as compared to  $746.60 \pm 93.78$  minutes in group RD. The difference in the mean duration of analgesia was statistically highly significant ( $p\text{-value} < 0.05$ ) (Table 2). Intraperitoneal injection for pain relief after laparoscopic cholecystectomy has shown conflicting results as dose and concentration, site of instillation and timing of instillation (before or after) of the anesthetic solution, residual CO<sub>2</sub>, spillage of bile and blood, instillation in head-down position versus supine position and postoperative analgesia regimen. The results were in concordance with studies conducted by Patel HS et al [17], Tripathkaur Bindra et al[18] Devalkar et al [12]. Although Ranjita Acharya et al[14] found that dexmedetomidine prolong duration of analgesia however mean duration was less as compare to the present study since dexmedetomidine ( $1\mu\text{g}/\text{kg}$ ) was added to



ropivacaine and also infiltrated drug at port site to block somatic component of pain to prolong the mean duration of analgesia. Devalkar et al [12] found mean duration of analgesia (8 hours) less as compared to this study, one reason could be, bupivacaine 0.25% 30ml for intraperitoneal instillation also for periportal infiltration they used lignocaine 2%. In the present study, the drug was instilled intraperitoneally in 20 degree Trendelenburg position and kept it for 20 mins and was one of the contributory factor for good pain relief. In laparoscopic cholecystectomy, reverse trendelenberg position is required. It directs intraperitoneal local anaesthetics away from cholecystectomy wound and prevents its flow over the coeliac plexus and phrenic nerve endings. Therefore it cannot attain sufficient concentration to block the nociceptive input.

In the present study total number of doses of rescue analgesic required were less in group RD as compared to Group R (Figure 2). Ranjita Acharya et al [16] also showed similar results. These findings suggest that adding dexmedetomidine to bupivacaine intraperitoneally significantly decreases analgesic requirement. The above results were in agreement with that of Ahmed et al [4], Sunil Chiruvella et al [20], Shukla et al [15]. Shukla et al. concluded that intraperitoneal instillation of dexmedetomidine in combination with bupivacaine gives better pain relief and reduces analgesic requirement as compared to bupivacaine alone in laparoscopic cholecystectomy. Shoulder tip pain after laparoscopic cholecystectomy occurs in 35%- 63% of patients [19]. The proposed mechanism of shoulder pain seems to be a diaphragmatic stretching with phrenic nerve neuropraxia. In the present study, shoulder tip pain was observed only in 2 patients in group R and none in group RD (Table- IV). Similar results were found in Sunil Chiruvella et al [20], Ranjita Acharya et al [16], Devalkar et al [12] studies. Regarding adverse effects, nausea and vomiting were found in 3 patients in Group R, 1 patient in Group RD. The cause could be higher pain scores and thus greater autonomic response in Group R. Similar findings were obtained by Kucuk et al [6] study.

The present study showed no significant difference in Mean heart rate, mean arterial pressure and Mean SpO<sub>2</sub> between the two groups at any time interval postoperatively (p value > 0.05) [Figure III, IV]. Rescue analgesia was given on demand whenever VAS score reached 4, hence rise in blood pressure due to pain was not prominent in any of two groups. Study done by Kim et al [21] revealed same finding. Sedation was assessed using Ramsay sedation score at 0, 0.5, 1, 2, 4, 6, 12 and 24 hours in both the groups. On intergroup analysis, mean sedation score in the postoperative period was found to be less than 2 at all time interval in both R and RD groups and was observed to be statistically insignificant (p-value > 0.05) (Table III). Previous study done by Chilkoti GT et al 2019, [10] evaluated the sedative effect of dexmedetomidine intraperitoneally, compared three groups, Group I administered intravenous dexmedetomidine with intraperitoneal ropivacaine, In Group II intraperitoneal bupivacaine alone & Group III dexmedetomidine bupivacaine intraperitoneally. Sedation scores were statistically significantly higher in iv dexmedetomidine group in first two hrs. Intergroup analysis revealed mean sedation score < 1 at different time intervals in all three Groups. This could be attributed to elimination half-life of dexmedetomidine (2-3 hrs). In the present study, mean sedation score was high in RD group as compared to R group but not statistically significant, which maybe attributed to its local action. IP administration of dexmedetomidine causes local

analgesia by enhancement of the hyperpolarization-activated cation channels, which prevents the nerve from returning to resting membrane potential. There was no incidence of bradycardia, hypotension and pruritus, in the two groups (Table 4)]. Similar findings were obtained by Sunil Chiruvella et al[20].

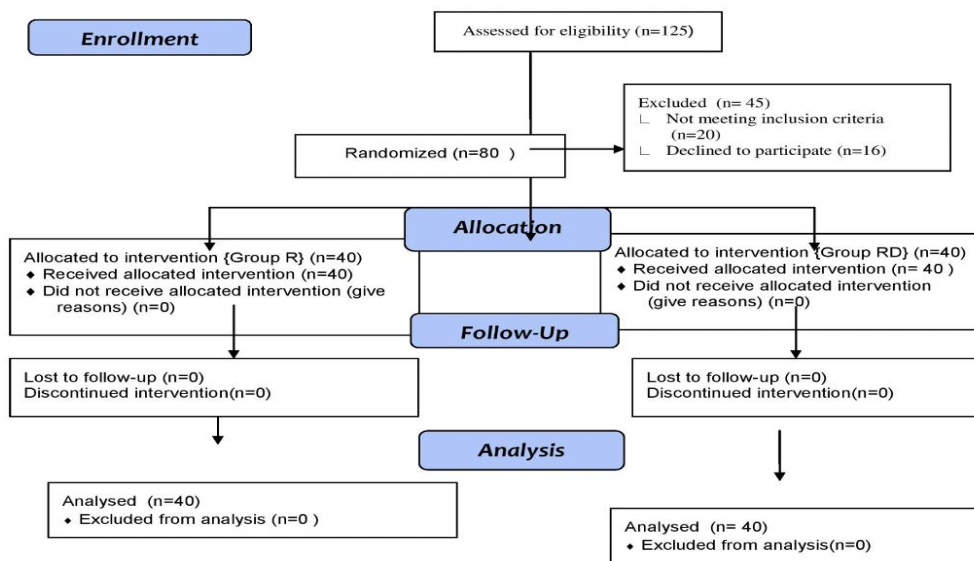
### Limitations

Postoperative pain is a highly subjective experience, no quantifiable objective assessment was done. The population enrolled was in the age group of 18-60 years which were otherwise healthy patients of ASA Grade I and II, so the effect of Dexmedetomidine as an adjuvant in older patients with cardiovascular co morbidities is yet to be investigated. Total analgesic consumption could have been ascertained more precisely if the study were conducted for longer periods and sample size was large. Also the duration of hospital stay was not noted which is a key variable to measure health in economic term.

### Conclusion

The study concludes that dexmedetomidine 1 $\mu$ g/kg may be used as adjuvant to 0.25% ropivacaine for effective post-operative analgesia in laparoscopic cholecystectomy. Intra-peritoneal instillation of 0.25% Ropivacaine with dexmedetomidine provides superior and prolonged pain relief without any adverse effects, making its use simple, safe and effective for postoperative analgesia in patients undergoing laparoscopic cholecystectomy under General Anaesthesia.

#### CONSORT DIAGRAM



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