COMPARATIVE STUDY OF THE EFFECT OF INTRAPERITONEAL INSTILLATION OF ROPIVACAINE 0.75% 10ML, AND ROPIVACAINE WITH DEXMEDETOMIDINE 1 MCG/KG FOR POST-OPERATIVE ANALGESIA AFTER LAPAROSCOPIC CHOLECYSTECTOMY

Ragu K[1], Sandeep Shankar[2], Ravi kumar[3]

[1]Assistant Professor, Department of Anesthesiology, Mmch & Rc, Modakkallur Ulliyeri, Calicut, India.
[2]Associate Professor, Department of Anaesthesia, Yenepoya Medical College Mangalore
[3]Professor, Department of Anesthesia, MMCH &RC, Modakkallur, Kozhikode, India.

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Corresponding Author: Dr Ragu K, Assistant Professor, Department Of Anesthesiology , Mmch & Rc, Modakkallur Ulliyeri, Calicut, India.

ABSTRACT

Background: Cholecystectomy is one of the most common operative procedures performed in field of general surgery. Present study was aimed to compare the post-operative analgesic effect of intra-peritoneal instillation of ropivacaine 0.75% alone and ropivacaine with dexmedetomidine 1 mcg/kg after laparoscopic cholecystectomy. **Material and Methods:** Present study was single-center, prospective, comparative study, conducted in patients age between 18 and 60 years, ASA grade I or II, posted for elective laparoscopic cholecystectomy. Participants were divided in to two categories as Group R (Ropivacaine alone) & Group RD (Ropivacaine and dexmedetomidine). **Results:** Both groups were comparable in terms of age, weight, and gender distribution (p-value> 0.05). Baseline hemodynamic parameters were comparable in both the groups. There were no significant differences in the mean HR, mean SBP, mean DBP, mean MBP and mean SpO2 between the two groups at any time interval. (p- value> 0.05). The duration of analgesia (Mean ±SD) was longer in group RD (746.60 ±93.78) compared to group R (525.80 ±66.64) it was statistically highly significant. (p-value< 0.0001). The total number of doses of rescue analgesic required was lesser in group RD in comparison to group R. Total analgesic consumption in 24 hours was lesser with 0.75% ropivacaine with dexmedetomidine (84.38 ±25.12mg) as compare to 0.75% ropivacaine (150.0 ± 37.98 mg). Mean VAS scores were higher in group R than in group RD at all the time intervals and it was statistically highly significant. (p-value<0.05). The incidence of Shoulder pain (5 %) was seen only in group R, compared to group RD. In postoperative complications, the PONV was observed in 3 patients (7.5 %) among patients in Group R compared to one patient (2.5%) in group RD. **Conclusion:** We recommend the use of dexmedetomidine as additive to ropivacaine for intra-peritoneal instillation, as it significantly prolongs duration of analgesia along with minimal side effects.

Keywords: dexmedetomidine, ropivacaine, post-operative analgesia, laparoscopic cholecystectomy.

INTRODUCTION

Cholecystectomy is one of the most common operative procedures performed in field of general surgery. In present days, laparoscopic cholecystectomy is preferred over open cholecystectomy due to facts such as minimally invasive procedure, achieve cosmetic results, reduce complications like hemorrhage, relatively fast recovery, reduce hospital stay, less prone to post- operative infections, less severity of pain, minimizes use of(or) dependence on

post-operative oral analgesics.[1,2]

Several literatures illustrate multiple modes and approaches to overcome the pain. Use of Non-Steroidal Anti Inflammatory Drugs (NSAIDS)/Parenteral analgesics/Opioids, local anaesthetic instillation, alpha 2 agonists has marked a tremendous change in pain management. The advantage of using local anesthetics is that, it provides adequate analgesia without drastic complications. Instillation of local anesthetic in to peritoneal cavity, blocks visceral afferent signaling and modifies visceral nociception and illness responses.[3,4]

The backbone of intraperitoneal local analgesic instillation is "preemptive analgesia" which refers that previously administered medications modulate the arousal of nociception action in the post-operative period sparing pain-after analgesics.[5] The preemptive analgesia prevents the formation of central sensitization to painful stimuli by decreasing response from pain sensation. Present study was aimed to compare the post-operative analgesic effect of intra-peritoneal instillation of ropivacaine 0.75% alone and ropivacaine with dexmedetomidine 1 mcg/kg after laparoscopic cholecystectomy.

MATERIAL AND METHODS

Present study was single-center, prospective, comparative study, conducted after approval from institutional ethical committee, informed written consent was obtained from the patients.

Inclusion criteria

- Patients age between 18 and 60 years, ASA grade I or II, posted for elective laparoscopic cholecystectomy, willing to participate in present study

Exclusion criteria

- Patients undergoing emergency surgery
- Patient refusing surgery
- Allergy to trial drugs
- History of alcohol and drug abuse
- Pregnancy, cardiovascular, hematological, neurological, respiratory disease

Pre-anaesthetic check-up was done the day before surgery. All patients underwent complete history taking, measurement of height and weight of the patient, vitals including pulse rate, spo2, blood pressure, respiratory rate, detailed systemic examination – cardiovascular system, respiratory system, central nervous system, gastrointestinal system & examination of airway.

Routine hematological investigations like Hb%, TLC, DLC, ESR, Platelet count, Blood sugar (fasting and post prandial), Serum Urea and Creatinine, Chest X- ray, Urine-Routine and microscopy & ECG were done in each patient. Patient was kept fasting for 8 hours before surgery.

All patients were transported to the operating room without premedication. After arriving to operating theatre, an 18 gauge IV cannula was inserted; Monitors like SpO2, ECG, NIBP were attached and baseline values SBP, DBP, SpO2, pulse rate, EtCO2 were recorded. All patients were premedicated with injection glycopyrrolate 0.004 mg/kg and injection tramadol 2mg/kg. Preoxygenation with 100% O2 was done for 3 min. GA was induced with injection propofol 2.0 mg/kg followed by injection succinyl choline 2mg/kg to facilitate orotracheal intubation. The trachea was intubated with a cuffed orotracheal tube of appropriate size. Anaesthesia was maintained with oxygen and 1–2% sevoflurane. Vecuronium bromide 0.1mg/kg bolus followed by 1mg intermittently was used to achieve muscle relaxation. Minute ventilation was adjusted to maintain normocapnia (end tidal CO_2 between 34 and 38 mm Hg) and EtCO2 was monitored.

Nasogastric tube of appropriate size was inserted. Hypotension/hypertension was defined as fall/rise in SBP of >20% from the baseline values and bradycardia/tachycardia was

defined as fall/rise in pulse rate of >20% from the baseline values. Haemodynamic fluctuations were to be managed accordingly. Patients were placed in reverse Trendelenburg's position (15-20°) with position tilted to left side. Intra-abdominal pressure was maintained 10-12 mm Hg during laparoscopy.

Patients will be randomly allocated to one of the groups using table of randomisation,

- Group R (*n*=50) – received-intraperitoneal instillation of 0.75% ropivacaine 10ml + 5ml normal saline
- Group RD (*n*=50) – received-intraperitoneal instillation of 0.75% ropivacaine 10ml + dexmedetomidine 1µg/kg making the volume 5 ml with normal saline

All patients received infiltration of 20mL of 0.75% ropivacaine at trocars insertion site, being 6mL in the umbilical incision, 6mL in the epigastric incision and 4mL in both working portals after removal of trocar.

An anaesthestist not involved in the study, prepared the study drugs. The anaesthetist who observed the patient and surgeon was not aware of the study group until the end of the study. Peritoneal wash was done at the end of the surgery. Before removal of trocar in Trendelenburg's position, the study solution was given intraperitoneally; equally into the hepatodiaphragmatic space, on gall bladder bed and near and above hepatoduodenal ligament; CO_2 evacuated. All patients also received infiltration of study drug at trocars insertion site at umbilical incision, epigastric incision, and both working ports after trocar removal. The neuromuscular blockade was antagonized with neostigmine 0.05 mg/kg and glycopyrrolate0.01mg/kg and patients were extubated. The NG tube was removed, and the patient was shifted to Recovery Room. All patients stayed in Recovery Room for 2 h after the end of surgery.

The postoperative pain was assessed using 10 point VAS at 0.5 ,1, 2, 4, 6, 8 ,12, 24 hrs. after surgery and over all VAS score.(VAS score 0 no pain ,VAS score 10 worst possible pain) Haemodynamic parameters (SBP, DBP, MBP, Pulse, SpO_2)-were recorded at 0.5, 1, 2, 4, 6, 8, 12, 24 hrs. postoperatively. Patients were regularly monitored for episodes of hypotension (MAP<60 mmHg), and bradycardia (HR<60bpm) in post-operative period.

Rescue analgesic – Inj. diclofenac aqueous (75 mg IV) was given when VAS > 4.Time to first analgesic requirement (considering the extubation as time 0) and total analgesic consumption in the 24 hours postoperative period were noted. Patients were also observed for postoperative nausea and vomiting. Patients who complained of nausea or vomiting were given injection ondansetron 4 mg IV. Any complication and side effects were recorded

The statistical analysis will be carried out using IBM SPSS (Statistical Package for Social Sciences) statistical version 21. The analysis includes frequency table, bar, pie chart, association of variables based on Chi-square. All quantitative variables will be estimated using measures of central location "mean" and measures of dispersion (standard deviation). For normally distributed data, Mean will be compared using independent t-test (for two groups). For not normality distributed data, Median will be compared using Mann Whitney U test (for two groups). For relationship Pearson Correlation method will be used using chi square test. Data analysis will be done in IBM SPSS 20.0

RESULTS

The present study was conducted among 100 patients to evaluate the efficacy of Ropivacaine and dexmedetomidine over Ropivacaine alone. Participants were divided in to two categories

Group R – Ropivacaine alone

Group RD - Ropivacaine and dexmedetomidine

Mean age in group R is 40.78±11.45 and in Group RD is 38.26±12.2. Statistical analysis shows no significant difference in average age among the two groups. (P>0.05). In group R there were 7 (14%) males and 41 (82%) females. Group RD had 10 (20%) males and 40

(80%) females. Statistical analysis shows no significant difference in average taken for gender distribution among two groups (p value > 0.05)

Both the groups were comparable in terms of mean weight with group R having 55.2±6.12 And group RD having 55.8±5.29 (p-value >0.05).

Table 1: General characteristics

(Mean ± SD)	Group R (n=50)	Group RD (n=50)	p-value	Significance
Age in years	40.78±11.45	38.26±12.2	0.29	NS
Weight (Kg)	55.2±6.12	55.8±5.29	0.60	NS
Gender				
Male	7 (14 %)	10 (20 %)	0.48	NS
Female	43 (86 %)	40 (50 %)		

There was no significant difference in the mean heart rate, systolic blood pressure (SBP), diastolic blood pressure (SBP), mean arterial pressure (MAP) & SpO2 between the two groups at any time interval (p> 0.05)

The mean duration of analgesia was 525.80 ± 66.64 min in group R while in group RD, the mean duration of analgesia was 746.60±93.78 min, difference in the mean duration of analgesia was statistically highly significant (p <0.05).

Table 2: Comparison of Mean Duration of Analgesia in Two Groups (MEAN±SD)

	Group R (n=50)	Group RD (n=50)	p-value	Significance
Duration of Analgesia (min)	522.6 ± 65.98	748.2 ± 91.87	<0.0001	HS

Mean VAS scores were lesser in group RD than in group R at all the time intervals and were statistically highly significant (p <0.05).

Table 3: Comparison of Post-Operative Mean Pain Score (VAS) in Two Groups

Time interval (hours)	MEAN VAS SCORE		p-value	Significance
	Group R (n=50)	Group RD (n=50)		
0	0 ± 0	0±0		
0.5	1.44 ± 0.54	0.3±0.46	<0.001	HS
1	2.02 ± 0.51	0.66±0.56	<0.001	HS
2	2.48 ± 0.5	1.34±0.63	<0.001	HS
4	2.94 ± 0.24	1.9±0.36	<0.001	HS
6	3.02 ± 0.25	2.08±0.4	<0.001	HS
12	2.54 ± 0.71	2.18±0.8	0.019	HS
24	3.5 ± 0.54	2.02 ±0.38	<0.001	HS

The total number of doses of rescue analgesic required was lesser in group RD as compared to Group R. In Group R 10 patients (25 %) required 3 doses of rescue analgesic, whereas none of the patients required 3 doses of rescue analgesic in Group RD. In Group R, 2 doses were required in 25patients (62.50%), 1 dose in 5 patients (12.50%). In Group RD, 5 patients (12.50%) required 2 doses and 35(87.50%) patients required only one dose of rescue analgesic.

Table 4: Number of Doses of Rescue Analgesic Required (in 24 Hours)

Number of Doses	Group R (n=50)		Group RD (n=50)		p-value	Significance
	No. of patients	%	No. of patients (n)	%		
One	6	12%	44	88 %	<0.0001	HS
Two	37	74%	6	12%	<0.0001	HS
Three	7	14%	0	0	<0.0001	HS
Mean ± SD	2.02 ±0.51		1.12 ±0.33		<0.0001	

The mean total rescue analgesic consumption was low in group RD(84.0 ±24.62) as compared to Group R(151.5 ±38.6), and was statistically highly significant (p <0.05).

Table 5: Mean Amount (mg) of Rescue Analgesic Required in Two Groups (in 24 Hours)

	Group R (n=50)	Group RD (n=50)	p-value	Significance
Mean amount (mg) of rescue analgesic	151.5 ±38.6	84.0 ± 24.62	<0.0001	HS

Shoulder pain was complained by two patients in Group R (5%) as compared to none of the patients in Group RD.

Table 6: Comparison of Shoulder Pain

Shoulder pain	Group R (n=50)		Group RD (n=50)	
	n	%	n	%
	3	6	0	0

Chi square value=3.09 P=0.078 NS

The PONV was observed in 3 patients (7.5%) in Group R compared to 01(2.5%) in group RD.(p-value>0.05) There was no incidence of bradycardia, hypotension and pruritus in the two groups.

Table 7: Comparison of Adverse Effects

	Group R (n=50)		Group RD (n=50)		p-value	Significance
	N	%	n	%		
PONV	3	7.5	1	2.5	*P*= 0.16	NS

Chi square value = 1.89,

Mean sedation score in postoperative period was found to be less than 2at all time interval, also on intergroup comparison the difference in the RSS between the two groups were observed to be statistically insignificant(p-value> 0.05) (Unpaired t test)

Table 8: Comparison of Sedation Score (RSS) in Two Groups

Time interval (hours)	Mean RSS Score		p-value	Significance
	Group R (n=50)	Group RD (n=50)		
0	2 ±0.45	2.14 ± 0.57	0.177	NS
0.5	1.84 ±0.37	1.9 ± 0.3	0.377	NS
1	1.84 ±0.37	1.9 ± 0.3	0.377	NS
2	1.82 ±0.39	1.88 ± 0.33	0.406	NS
4	1.8 ±0.4	1.88 ± 0.33	0.28	NS
6	1.72 ±0.45	1.84 ± 0.37	0.15	NS

DISCUSSION

Pain after surgical procedures is due to peritoneal inflammation from tissue trauma caused by surgical incision and dissections, nerve injuries caused by transaction, stretching, or compression. Pain occurs as a result of stretching of the intra-abdominal cavity, diaphragmatic irritation (action of residual in CO_2 in peritoneal cavity), gas insufflation and raised intra peritoneal pressure.

The pain following laparoscopic and open cholecystectomy is visceral and parietal/somatic respectively. Parietal pain is sharp and can be localized by specific spot or

point. Visceral pain is dull, non- localised, occurs when the nerves through the walls of an organ are stretched. If irritation of parietal peritoneum occurs, visceral pain may lead to somatic/ parietal pain. The intensity of pain following open cholecystectomy is higher than pain following laparoscopic cholecystectomy. Uncontrolled post- operative pain causes venous thrombo-embolism, it may lead to chronic regional pain syndromes

Ropivacaine is considered as classical example of local anesthetic with anaesthetic and analgesic effect. Ropivacaine is a safest Food and Drug Administration (FDA) approved long acting amino- amide local anaesthic.[6] The salient features are less lipophilic, less cardio and neuro-toxic, low probability of penetrating large myelinated motor fibres and tolerable. It causes reversible inhibition of sodium ion influx and blocks propagation of action channels.

Dexmedetomidine an alpha 2 agonist acts as an adjuvant and has a synergistic effect with ropivacaine. It intensifies the motor blockage, prolongs duration of analgesia, and causes sedation without markable respiratory depression.[7] It blocks substance P in the nociceptive pathway and acts on inhibitory G protein, thereby it increases the conductance through potassium channels.

The mean duration of analgesia was 525.80 ±66.64 min in group R with a range of 360 to 620 min. In group RD, the mean duration of analgesia was 746.60 ±93.78 min with a range of 510 to 845 min. The difference in the mean duration of analgesia was statistically highly significant ($p < 0.05$).

At 0.5 hours, Group R had a mean VAS of 1.44 ±0.54, while Group RD showed 0.3 ± 0.46. The mean VAS at 1 hour; Group R showed 2.02 ± 0.51, whereas Group RD showed 0.66 ± 0.56. At 24 hours Group R and RD showed VAS of 3.5 ± 0.54 and 2.02 ± 0.38 respectively. The mean VAS scores were lesser in group RD than in group R at all the time intervals and were statistically highly significant ($p < 0.05$).

Yeh CN *et al.*,[8] found that combined wound and intraperitoneal local anaesthetic after laparoscopic cholecystectomy significantly decreased the immediate postoperative pain.

Shrinivas Rapolu *et al.*,[9] compared the analgesic effect of intraperitoneal instillation of dexmedetomidine with 0.25 % bupivacaine (125 mg) 50ml v/s 0.25% bupivacaine (125mg) 50ml alone. There was statistically significant difference in VAS pain score at 6, 8, 12, 18, 24 hours after surgery in group BD (3.21 ±0.83) compared to group B (2.81 ±0.91) up to 24 hours. Time to requirement of first dose rescue analgesia for group BD was 7.61 hours compared to 5.81 hours for group.

In another study, Gopal Reddy Narra *et al.*,[10] showed results that post- operative VAS pain scores were significantly lower in levobupivacaine 0.25% (39.58%) when compared to ropivacaine (52.08%).

Dr. Hitesh Kumar S. Patel *et al.*,[11] also showed a statistically significant difference in VAS at six hours after surgery in group BD (3.14 ±0.40) compared to group B (4.12 ±0.82) up to 24 hours. Neha T Das *et al.*,[12] also did a study showing intraperitoneal infiltration of LA significantly reduces pain intensity score in early postoperative period and helps in improving the postoperative recovery after laparoscopic cholecystectomy.

The total number of doses of rescue analgesic required was lesser in group RD (1.12 ± 0.33) as compared to Group R (2.02 ± 0.51). In Group R, 10 patients (25 %) required 3 doses of rescue analgesic, whereas none of the patients required 3 doses of rescue analgesic in Group RD. In Group R 2 doses were required in 25 patients (62.50%), 1 dose in 5 patients (12.50%). In Group RD, 5 patients (12.50 %) required 2 doses and 35 (87.50%) patients required only one dose of rescue analgesic. The mean total rescue analgesic consumption was low in group RD (84.0 ± 24.62 mg) as compared to Group R(151.5 ± 38.6 mg), with a p value of 0.0001 and was statistically highly significant ($p < 0.05$).

Narasimhan *et al.*,[13] showed similar results that intraperitoneal instillation of dexmedetomidine in combination with bupivacaine in elective laparoscopic cholecystectomy

was more effective as an analgesic compared to bupivacaine alone or in combination with tramadol.

Shoulder pain was complained by two patients in Group R (5%) as compared to none of the patients in Group RD. Shivhare P *et al.*,[14] did a randomized double blind study showing that intraperitoneal instillation of ropivacaine reduces the incidence and intensity of upper abdominal pain and shoulder tip pain after laparoscopic cholecystectomy

A Singh *et al.*,[15] concluded that ropivacaine with fentanyl reduces not only the intensity of visceral, parietal and shoulder pain but also the total rescue analgesic dose consumption. The post-operative nausea and vomiting was observed in 3 patients (7.5%) in Group R compared to one (2.5%) in group RD (p-value > 0.05). There was no incidence of bradycardia, hypotension and pruritus in the two groups. Chhavi S Sharma *et al.*,[16] did a randomized prospective double blinded study concluding that intraperitoneal analgesia with local anaesthetic (ropivacaine and bupivacaine) is simple, effective method with minimal side effects.

The mean sedation scores at 1 hour were 1.84 ±0.37 and 1.9 ±0.3 for Group R and Group RD respectively. Mean sedation score (RSS) in postoperative period was found to be less than 2 at all-time intervals; Also, on intergroup comparison the difference in the RSS between the two groups were observed to be statistically insignificant(p-value> 0.05) (Unpaired t test).

Limitations of study were that pain is a highly personal experience and its ambiguity lies in that it is a subjective sensation and thorough objective observation of such is difficult. 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.

CONCLUSION

From our study we concluded that dexmedetomidine 1µg/kg can be used as adjuvant to 0.75% ropivacaine for effective post-operative analgesia in laparoscopic cholecystectomy. Intra-peritoneal instillation of 0.75%ropivacaine with dexmedetomidine provides superior and prolonged pain relief without any adverse effects, making its use simple, safe and effective for postoperative analgesia in laparoscopic cholecystectomy.

We recommend the use of dexmedetomidine as additive to ropivacaine for intra-peritoneal instillation and port site infiltration in patients posted for elective laparoscopic cholecystectomy, as it significantly prolongs duration of analgesia along with minimal side effects.

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