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Comparison of Efficacy of Intraperitoneal Instillation of Ropivacaine with Ropivacaine Dexmedetomidine Combination for Post-Operative Analgesia Following Laparoscopic Cholecystectomy

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Abstract

Background and Aims: Intraperitoneal instillation of local anaesthetics is one of the recent techniques to minimize post-operative pain after laparoscopic surgeries. We compared the effects of intraperitoneal instillation of ropivacaine dexmedetomidine combination with that of intraperitoneal ropivacaine alone in patients undergoing laparoscopic cholecystectomies. *Methods:* A total of 120 patients participated in this prospective, randomized, doubleblinded study. Patients were divided into two study groups(n=60) randomly and received intraperitoneal instillation of ropivacaine (0.25%) 50 ml in Group R and ropivacaine with dexmedetomidine 1 μg/kg, (diluted to 50ml volume with normal saline) in Group RD at the end of surgery under sterile precautions. Visual analogue scale score (VAS) was used to assess the quality of analgesia at various intervals. Time to the first demand for analgesia, total dose of analgesic used in the first 24 hours and adverse effects if present were noted. Statistical analysis was performed with the Student's t-test and Chi-square test (level of significance $P = 0.05$). *Results:* VAS pain scores at different time intervals was significantly lower, time to first demand analgesia (min) in the post-operative period was increased and total post-operative analgesic consumption (mg) was lesser in group RD than group R. Also, mean heart rate and mean blood pressure were significantly lower in group RD than in group R. There was no statistically significant difference regarding the adverse effects between the groups. *Conclusion:* End operative intraperitoneal instillation of ropivacaine dexmedetomidine combination is superior to ropivacaine (alone) for post-operative analgesia in laparoscopic cholecystectomy.

Keywords: Dexmedetomidine; Intraperitoneal; Laparoscopic Cholecystectomy; Post Operative; Ropivacaine.

Introduction

Laparoscopic cholecystectomy is currently the most widely practiced surgical procedure for cholelithiasis compared to traditional open cholecystectomy. In general, laparoscopic procedures have many advantages over open procedures such as minimal scar, lesser intensity and duration of post-operative pain and lesser incidence of hospital acquired infections thereby reducing the duration of hospital stay and are cost effective as well [1]. Pain in laparoscopic procedures is due to stretching of the parietal peritoneum, peritoneal and diaphragmatic irritation, all caused by pneumoperitoneum using carbondioxide during the procedure [2]. Systemic opioid analgesics and non-steroidal anti-inflammatory drugs (NSAID) are frequently used to relieve post-operative pain following laparoscopic cholecystectomy. Adverse effects like respiratory depression, pruritus, constipation, gastritis, nephrotoxicity, nausea and vomiting are very common in such cases [3]. Epidural analgesia also is not very promising in relieving the post-operative pain in these surgeries. Intraperitoneal instillation of local anaesthetic agents alone or combined with additives like opioids such as morphine, buprenorphine or with α-2 agonists such as clonidine and dexmedetomidine have been found to be effective in reducing post-

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operative pain in these surgical procedures [4]. The aim of this study was to compare the effects of end-operative intraperitoneal instillation of ropivacaine dexmedetomidine combination with that of intraperitoneal ropivacaine in patients undergoing laparoscopic cholecystectomies.

Methods

This study was done in a 1500 bedded multispecialty teaching hospital from august 2015 to january 2017. After getting approval from Institutional Ethical Committee, written informed consent was obtained from all the patients during the pre anaesthetic checkup before surgery. One hundred and twenty patients belonging to American Society of Anaesthesiologists classification (ASA) physical status I and II of age between 18 and 60 years and of both sexes were included in this prospective, randomized, doubleblinded study. Exclusion criteria included patient refusal, patients with allergy to study drugs, patients with physical status ASA III and above, patients on anti-hypertensive drugs and β blockers, those in whom procedure had to be converted to open cholecystectomy and in whom abdominal drain was inserted. Lot method was used to randomly allocate the patients to one of the two groups, group R (n = 60) and group RD (n = 60). On arrival to operating room, an 18gauge intravenous (IV) catheter was inserted on patient's fore arm and monitoring of oxygen saturation (SpO2), electrocardiography and non-invasive blood pressure was started and baseline values were recorded.). Pre-medication was done with inj fentanyl 2 μg/kg, inj glycopyrolate 0.2 mg and inj ondensetron 4 mg through IV. Pre-oxygenation was done for three minutes with 100% oxygen (O2).Patient was induced with IV propofol 2 to 2.5 mg/kg followed by succinyl choline 2 mg/kg for muscle relaxation. The trachea was intubated with a cuffed endotracheal tube of appropriate size, lubricated with lignocaine jelly 2%. Anaesthesia was maintained by using 66% N2O in oxygen with isoflurane as the volatile agent. Intermittent maintenance dose of atracurium besylate was used to facilitate muscle relaxation. End tidal carbondioxide [EtCO2] was monitored and was maintained between 34 and 38 mm Hg by adjusting minute ventilation. Fluctuations in haemodynamic parameters like hypotension, hypertension (hypotension/hypertension was defined as fall/rise in systolic blood pressure of >20% from the baseline values), tachycardia and bradycardia (bradycardia/tachycardia was defined as fall/rise in pulse rate of >20% from the baseline values) were managed accordingly. During laparoscopy, intra-abdominal pressure was maintained between 12 and 14 mm Hg. At the end of the procedure, the CO2 was removed carefully by manual compression of the abdomen with trocar in situ. Under sterile precautions, the local anaesthetic solution was administered intraperitoneally before removal of trocar in Trendelenberg's position itself, into the hepato-diaphragmatic space and on the gall bladder bed. Group R (n = 60) received ropivacaine 0.5% solution 25 mL, diluted to 50 mL with normal saline andgroup RD (n = 60) received ropivacaine 0.5% 25 mL+ dexmedetomidine 1ìg/kg diluted to 50 ml with normal saline respectively. Neuromuscular blocked was reversed with neostigmine 0.05 mg/kg and glycopyrolate 0.01 mg/kg and was extubated and shifted to post-anaesthesia care unit (PACU). Study drugs were prepared by an anaesthesiologist who was not involved in this study. Anesthesiologist and residents who observed the patient in the PACU were also blinded regarding the study groups throughout the study. Post-operatively all patients were monitoredforv 24 hours in the PACU. The primary outcome variable of this study was to compare pain intensity between the two groups R and RD using VAS score. The secondary outcomes studied were time to first demand for analgesia, mean heart rate, mean arterial blood pressure and total dose of analgesic used in 24 hour post-operative period and adverse effects if any. The intensity of post-operative pain was recorded for all the patients using VAS score at 1, 2, 4, 6, 8,10,12,16 and 24 hours after surgery. All the study patients were instructed about the use of the VAS score assessment during pre-anaesthetic check- up (VAS score - no pain, VAS score 10 - worst possible pain). Patients who reported VAS 3 or more were given diclofenac 75 mg intramuscularly as rescue analgesia. Patients were also observed for post-operative nausea and vomiting. Patients who suffered nausea or vomiting were given ondensetron 4 mg IV. Time to the first demand analgesia from the extubation time, total dose of analgesia and adverse or side effects over 24 h postoperatively were noted. A total sample size of 120 patients (n = 60 each for groups) was calculated using error of 0.05 and power of 80%. A total of four patients were excluded from the study because of conversion to open procedure i.e. three patients in group R and one patient in group RD. Statistical analysis was performed using Statistical Package for Social Services®software (SPSS Version 20). Quantitative data was analyzed using student't' test

and qualitative data was analysis was done using Chi-square test. A 'p' value of less than 0.05 was considered as statistically significant.

Results

There was no significant difference with respect to age, sex, weight, ASA physical status and duration of surgery [Table 1].

Visual analogue scale at different time intervals were statistically significantly lower in group RD than group R except in the 24th hour [Table 2, Fig 1].

Mean post-operative heart rate and mean arterial pressure were significantly lower in group RD than group R till the 12th hour but not statistically significant in the 16th and 24th hour [Table 3&4, Fig 2 & 3].

Time to first demand analgesia was longer in group RD (124±24 min) as compared to R (67±20 min) and total diclofenac consumption was also lower in group RD (70±18 mg) than Group R (190 ±80 mg) [Table 5].

Table 1: Demographic characteristic of the study groups (mean±SD)

Variable	Group R (N=50)	Group RD (N=50)	P
ASA I	31	29	-
ASAII	19	21	-
Duration of Surgery (min)	70±12.05	72±9.87	0.3661

Table 2: Post-operative VAS score (mean±SD)over time

Time (Hours)	Group R (N=50)	Group RD (N=50)	P
1	4.104±1.70	2.015±0.97	0.0001
2	5.28±1.06	2.42±0.78	0.0001
4	5.97±1.07	2.11±0.24	0.0001
6	4.67±1.10	1.97±1.03	0.0001
8	4.01±0.91	1.86±0.57	0.0001
10	3.38±1.10	2.90±0.85	0.0164
12	3.06±0.81	2.57±1.30	0.0259
16	2.89±0.94	2.34±0.79	0.0021
24	1.76±1.20	1.49±0.85	0.1972

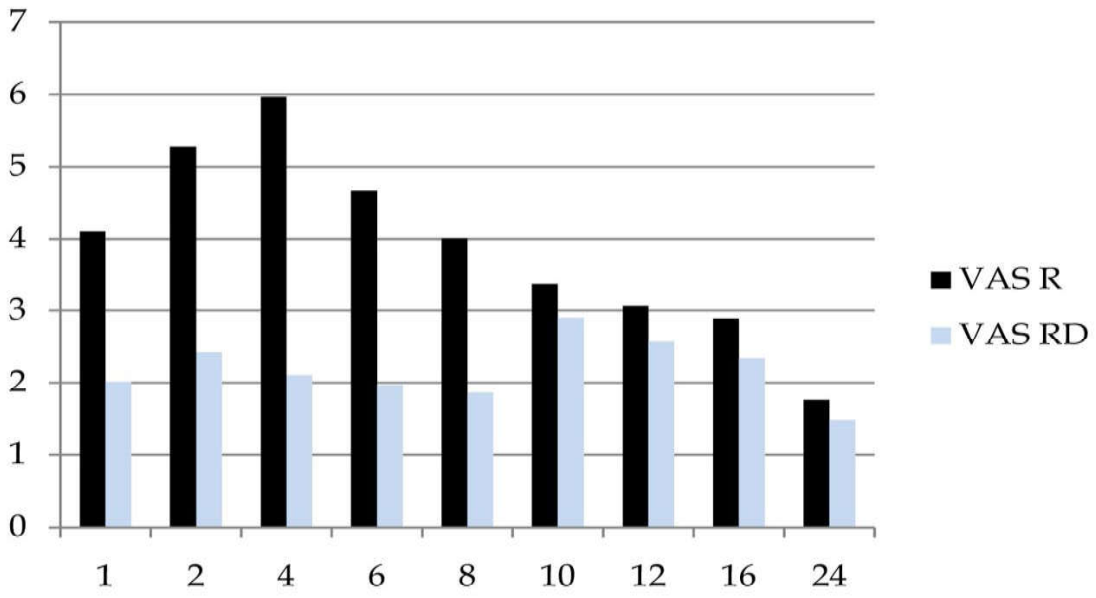

Fig. 1: Post-operative VAS score (mean±SD) over time

Table 3: Post-operative mean BP (mmHg) (mean±SD) over time

Time(Hours)	Group R (N=50)	Group RD (N=50)	P
1	94.56±6.78	89.3±5.45	0.0001
2	94.44±7.80	90.2±6.08	0.0001
4	95.5±5.89	88.9±4.34	0.0001
6	96.3±7.97	89.32±5.45	0.0001
8	94.56±8.76	90.56±5.09	0.0001
10	94.6±7.54	91.05±6.40	0.0127
12	95.4±6.98	91.4±4.86	0.012
16	93.2±7.04	90.6±5.01	0.359
24	90.4±5.95	89.8±5.20	0.5926

Table: 4: Post-operative mean heart rate (per minute) (mean±SD) over time

Time (Hours)	Group R (N=50)	Group RD (N=50)	P
1	66.67±4.61	63.24±4.90	0.0005
2	67.08±3.89	62.78±5.07	0.0001
4	69.5±4.80	60.57±4.36	0.0001
6	71.23±5.78	62.79±5.78	0.0001
8	74.04±6.45	63.5±7.56	0.0001
10	75.56±5.57	63.70±4.35	0.0001
12	72.67±6.70	66.45±4.01	0.0001
16	73.56±7.18	72.7±5.72	0.5092
24	74.05±5.47	74.56±4.85	0.6220

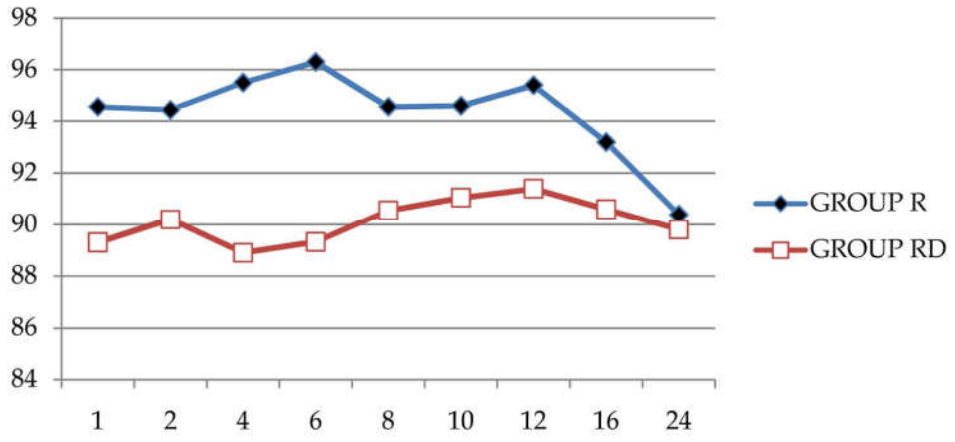

Fig. 2: Post-operative mean BP (mmHg) (mean±SD) over time

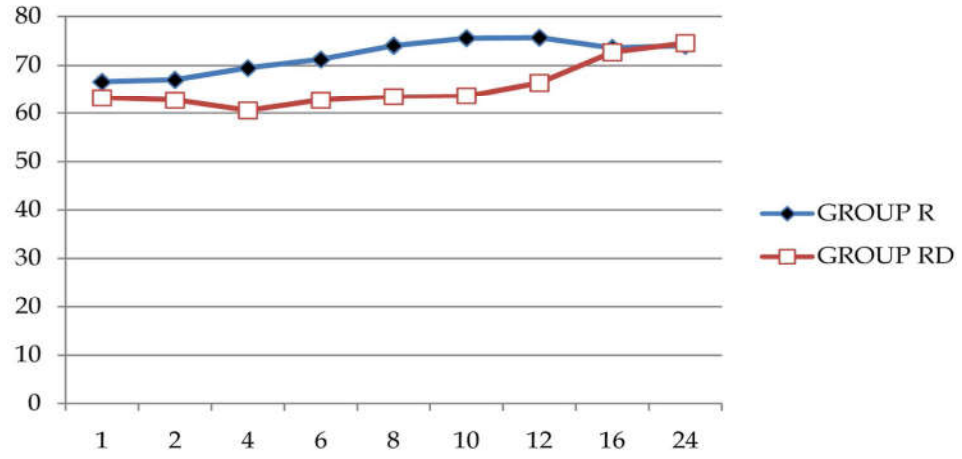

Fig. 3: Post-operative mean heart rate (per minute) (mean±SD) over time

Table 5: Time for first demand analgesia and analgesic requirements (mean±SD) in the study groups

Variable	Group R (N=50)	Group RD (N=50)	P
Time for first demand analgesia (min)	67±20	124±24	0.0001
Total dose of diclofenac (mg)	190 ±80	70±18	0.0001

Table 6: Post operative adverse effects (%) in the study groups

Variable	Group R (N=50) (%)	Group RD (N=50) (%)	P
Shoulder Pain	20 (40)	6(12)	0.1277
Nausea	10(20)	4(8)	df=4
Vomiting	6(12)	0	SE= 4.522

Discussion

Pain is one of the key factors which causes much stress to the patient in the post- operative period after any surgical procedure. It causes the release of potentially harmful stress hormones such as catecholamines, corticosteroids, interleukins, anti-diuretic hormone etc. This may cause a multitude of complications such as fever, tachycardia, hypertension, worsening of diabetes mellitus, myocardial infarction, cerebro vascular accidents, etc. It hinders early mobilization of patients thereby increasing the morbidity, hospital stay duration, as well as the cost of the treatment. Anaesthesiologists play a key role in reducing the post-operative pain effectively thereby preventing most of the complications. Laparoscopic cholecystectomy is preferred both by the surgeons as well as the patients as it provides minimal surgical scar, reduced post-operative pain, lesser morbidity and lesser duration of hospitalization compared to open cholecystectomy. Pain following laparoscopic cholecystectomy has three components namely visceral pain, parietal pain and referred shoulder pain. Visceral pain predominates as the incisions are small and surgical manipulation is minimal in laparoscopic surgeries [5]. Visceral pain is due to carbon di oxide insufflation and raised intraperitoneal pressure which causes peritoneal inflammation and neuronal rupture [6].

Various treatment modalities like parenteral opioids, parenteral NSAIDS and local skin infiltration are employedto reduce overall pain for patients undergoing laparoscopic surgeries. All parenteral medications, though effective are associated with adverse effects such as gastritis, nephrotoxicity, nausea, vomiting, respiratory depression, constipation etc. Intraperitoneal instillation of local anaesthetic drugs has become an important technique to control pain in post operative period as it is more effective because it blocks the afferent visceral pain signals. The local anaesthetic agents acts by affecting neuronal membrane associated proteins and inhibits the release and action of prostaglandins which inhibits neuronal inflammation which in turn stimulates the nociceptors [7]. Ropivacaine (l-propyl-22, 62-pipecoloxylidide hydrochloride), a new long-acting amide local anesthetic which is available as pure S-enantiomer, is related to bupivacaine in molecular structure with a lesser cardiac and neurotoxicity [8]. We selected ropivacaine in our study because it is a relatively long-acting local anaesthetic agent (6-12 h), with lesser motor blockade and cardio toxicity than that of bupivacaine [9,10,11]. Goldstein *et al*. compared the post-operative analgesic efficacy of intra-peritoneal instillation of 20 mL of 0.5% bupivacaine, 20 ml of 0.75% ropivacaine and normal saline in laparoscopic gynecologic surgery and found that bupivacaine and ropivacaine groups had significantly lesser post-operative pain thanthat of normal saline group [12]. The total amount of ropivacaine used in this study (50 mL of 0.25% i.e. 125 mg) is far below the maximum dose for infiltration anesthesia in an adult patient (3 mg kg [1] or 200 mg of plain solution) therefore measuring the plasma concentrations of ropivacaine is not necessary in this study [13]. Dexmedetomidine, an α_2 adrenergic agonist inhibits the release of substance P at the level of the dorsal root neuron and prevents norepinephrine release at nerve endings [14]. Although these actions have good analgesic effects but it is the local effects of dexmedetomidine is of much importance here, since it causes local vasoconstriction, which may result in higher concentrations of local anaesthetics near the nerves which will enhance analgesia. More over perineural dexmedetomidine increases the hyperpolarization-activated cation current, which prevents the nerve from returning from a hyperpolarized state to resting membrane potential for subsequent firing [15]. Sunil Chiruvella *et al* assessed the analgesic effects of intraperitoneal instillation of ropivacaine and dexmedetomidine in laparoscopic cholecystectomies and concluded that intraperitoneal

instillation of ropivacaine dexmedetomidine combination was found to be effective than ropivacaine alone [16].

In our study, there was a statistically significant differencein VAS pain scores between R and RD groups implying that ropivacaine-dexmedetomidine combination is more effective than ropivacaine alone.

Ropivacaine combined with dexmedetomidine significantly reduces the diclofenac consumption in the 24 hours post-operative period than ropivacaine alone. More over hemodynamic parameters like mean heart rate and mean arterial pressure were significantly lower in group RD and there was no bradycardia or hypotension which required intervention. There was no statistically significant difference regarding the adverse effects between the two study groups (P = 0.1277). Limitation in our study is that pain being a subjective experience could be difficult to quantify objectively and compare when studying various treatment options. Very few studies were done in the past on addition of dexmedetomidine to intraperitoneal ropivacaine; in future this study may widen the scope for further studies with different doses of dexmedetomidine and different concentrations of local anaesthetics for post operative pain relief with minimal adverse effects after laparoscopic surgeries.

Conclusion

We conclude that end-operative instillation of ropivacaine (0.25%) - dexmedetomidine (1 μg/kg) combination intraperitoneally in patients undergoing elective laparoscopic cholecystectomy significantly reduces the post-operative pain and analgesic requirement as well as gives better hemodynamic stability in the post-operative period as compared to ropivacaine(0.25%) alone.

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