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Intra peritoneal installation of Ropivacaine compared to Ropivacaine plus Tramadol and Ropivacaine plus Dexmedetomidine for analgesic efficacy in laparoscopic cholecystectomy

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Abstract
Background and Aims: *In laparoscopic surgeries, intraperitoneal instillation of local anesthetics alone or in combination with non-opioids is gaining popularity, for better post-operative pain relief. This study compared the analgesic efficacy with regard to quality and duration of post‑operative analgesia and also total amount of rescue analgesia required in 24 hrs using intraperitoneal Ropivacaine (R), Ropivacaine plus tramadol (RT) or Ropivacaine plus dexmedetomidine (RD).*
Methods: *In this study, 123 patients undergoing laparoscopic cholecystectomy were divided into three groups: Intraperitoneal Ropivacaine 50 ml 0.2% +5 ml normal saline (NS):Group R(n=37),Intraperitoneal Ropivacaine 50 ml 0.2% + Tramadol 1 mg/kg (diluted in 5 ml NS):Group RT(n=41) and intraperitoneal Ropivacaine 50 ml 0.2%+Dexmedetomidine 1μg/kg (diluted in 5 ml NS):Group RD(n=45) before removal of trocar at the end of surgery. The quality of analgesia was assessed by visual analogue scale score (VAS), time to first request of analgesia and total dose of analgesic in the first 24 hrs. Hemodynamic parameters and adverse effects in three groups over 24 hrs were also noted. Statistical analysis was performed using Microsoft (MS) Office Excel Software with the Chi‑square test and fisher's exact test (level of significance P = 0.05).*
Results: *The mean of VAS pain score after 0.5,1, 2, 4, 6, 12 and 24 hrs of surgery was less in RD group compared to other two groups, and the difference was statistically significant (P < 0.05). Mean time of 1st request of analgesia was 63.7 min in group R, 116.9 min in group RT and 141.8 min in group RD which was statistically significant (P < 0.05). The mean total rescue analgesia consumption of inj. diclofenac in group RD was 81.70 mg, 109.80 mg in group RT and 140.60 mg in group R in 24 hrs after surgery which was statistically significant (P < 0.05). There were no statistically significant differences in the secondary outcomes.*
Conclusion: *Intraperitoneal instillation of ropivacaine‑dexmedetomidine renders patients relatively pain‑free in first 24 hrs after surgery, with longer duration of pain‑free period and less consumption of rescue analgesic as compared to ropivacaine‑tramadol combination and ropivacaine only.*
Keywords: *laparoscopic cholecystectomy, Ropivacaine, Tramadol, Dexmedetomidine, visual analogue scale score (VAS).*

Introduction

Laparoscopic cholecystectomy has emerged over the open procedure as the gold standard for surgical treatment of symptomatic gallstones.[1,2,3] Laparoscopic cholecystectomy results in better surgical outcome in terms of reduced postoperative pain, morbidity and duration of convalescence compared to open cholecystectomy,[4,5] systemic complications and quality of life.[6] In laparoscopic cholecystectomy because of gas insufflation and raised intraperitoneal pressure, there is peritoneal inflammation and neuronal rupture with a linear relationship between abdominal compliance and resultant severity of post-operative pain.[7] Pain may be visceral or somatic, upper abdominal, lower abdominal or in shoulders as well.[8] The type of pain after laparoscopic surgery differs considerably from that seen after laparotomy. Whereas laparotomy results mostly in parietal pain, patients after laparoscopic cholecystectomy complain more of visceral pain that results from the stretching of intra-abdominal cavity, peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity.[9] Postoperative pains due to cholecystectomy may be transient and most of the time it lasts for 24 hours but may extend up to 3 days. Immediately after surgery, the intensity of pain is more in the first 24 hours and then decreases gradually.[8,10,11]

Postoperative analgesia is a major component of perioperative care and local anaesthetic techniques are more effective than systemic analgesia regardless of the operation and mode of delivery.[12] Intraperitoneal local anaesthetics alone or in combination with non-opioid analgesics have been used to reduce postoperative pain following laparoscopy. This might reduce adverse effects of opioids and postoperative pain as well.[13,14] Therefore, including wound infiltration as part of a non-opioid, multimodal analgesic regime is recommended. The local anaesthetic 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.[15]

Material and Methods

The present study was conducted in the department of Anesthesiology in Government Medical Collage Srinagar from October 2016 to December 2017. Patients of ASA physical status I-II of both sexes, aged between 18 and 60 years, weight between 40-100 kg undergoing routine laparoscopic cholecystectomy were included in this observational study. After getting approval from Institutional Ethical Committee, written informed consent was obtained from all the patients before surgery.

Patients who refused, patients having acute cholecystitis at the time of surgery, patients who were allergic to local anesthetic and study drugs, patients in whom procedure had to be converted to open cholecystectomy, patients in whom abdominal drain was put, ASA III and above patients, patients in whom procedure lasted for more than 1 hour, Pregnant and lactating females were excluded from the study.

All patients were transported to the operating room without premedication. On arrival to operating room, an 18‑gauge intravenous catheter was inserted and monitoring of electrocardiography, non-invasive blood pressure, oxygen saturation (SpO_2) was started and baseline values were recorded. Premedication was given as pantoprazole 40mg intravenously. Preoperative analgesia with Fentanyl 1micro gram intravenously was given just before induction. Pre-oxygenation with 100% oxygen (O_2) was done for 3 min. General anesthesia was induced with Propofol 2.0–2.5 mg/kg intravenously followed by Atracurium 0.5mg/kg intravenously to facilitate orotracheal intubation. The trachea was intubated with a cuffed orotracheal tube of appropriate size. Anesthesia was maintained with 60% N_2O in oxygen with 0.8–1% Isoflurane. Each patient received intraoperative analgesia as Paracetamal infusion 1gm. Intermittent boluses of

Atracurium were used to achieve muscle relaxation. Minute ventilation was adjusted to maintain normocapnia (end tidal carbon-dioxide [EtCO$_2$] between 32 and 38 mm Hg) and EtCO$_2$ was monitored. Nasogastric tube of appropriate size was inserted. Hemodynamic fluctuations were to be managed accordingly. Patients were placed in 15-20° reverse trendelenberg's position with the left side tilt position. During laparoscopy, intra-abdominal pressure was maintained 12-14 mm Hg. The CO$_2$ was removed carefully by manual compression of the abdomen at the end of the procedure with open trocar.

Patients were assigned to one of the Groups as per the methodology adopted.

- Those who received Intraperitoneal Ropivacaine 50 ml 0.2% +5 ml normal saline (NS): Group R (Ropivacaine).
- Those who received Intraperitoneal Ropivacaine 50 ml 0.2% + Tramadol 1 mg/kg (diluted in 5 ml NS): Group RT (Ropivacaine+ Tramadol).
- Those who received intraperitoneal Ropivacaine 50 ml 0.2% + Dexmedetomidine 1μg/kg (diluted in 5 ml NS): Group RD (Ropivacaine+ Dexmedetomidine)

At the end of the surgery, the study solution was given intraperitoneally before removal of trocar in Trendelenberg's position, into the hepato-diaphragmatic space, on gall bladder bed and near and above the hepatoduodenal ligament. The nasogastric tube was removed. The neuro-muscular blockade was antagonized with Neostigmine 0.05 mg/kg and Glycopyrrolate 0.01 mg/kg and trachea was extubated and the patient was shifted to post-anesthesia care unit (PACU).

Postoperative management and pain control

All patients stayed in PACU for 24 hr after the end of surgery. The primary outcome variable was to compare pain by visual analogue scale [VAS]) score and duration of analgesia (time to the first request of analgesia considering the extubation as time zero in the post-operative period), total dose of rescue analgesic used in 24 hr period post-operative period and to assess any inadvertent adverse effects.

The intensity of post-operative pain was recorded for all the patients using VAS score at 0.5, 1, 2, 4, 6, 12, 24 hrs after surgery and over all VAS score (mean of all VAS scores). All the study patients were instructed about the use of the VAS score before induction of anesthesia (VAS score 0 – no pain, VAS score 10 – worst possible pain). Patients who reported VAS 4 or >4 were given injection Diclofenac 75 mg intramuscularly as rescue analgesia. Patients who still had VAS 4 or more even after 1 hr of administration of injection Diclofenac were given injection Tramadol 50 mg intravenously as second rescue analgesia. Patients were also observed for sedation using Ramsay Sedation Scale post-operatively. Side effects like nausea, vomiting, shoulder pain, pruritis, hypotension and bradycardia or any other complication were also noted and were managed as per protocol.

Statistical methods and analysis

A total of 134 patients were included in this study out of which 11 patients were excluded on the basis of study design and exclusion criteria. A total sample size of 123 patients was available for study (Group R, RT and RD having 37, 41 and 45 patients). The recorded data was compiled and entered in a spreadsheet (Microsoft excel) and then exported to data editor of SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA). Statistical software SPSS (version 20.0) and Microsoft excel were used to carry out the statistical analysis of data. Continuous variables were expressed as mean ± standard deviation and categorical variables were summarized as percentages. Analysis of variance (ANOVA) were employed for intergroup analysis of data and for multiple comparisons, least significant differences (LSD) test were applied. Chi-square test or Fisher's exact test, whichever appropriate, was used for comparison of categorical variables. Graphically the data was presented by bar and line diagrams. A p- value of less than 0.05 was considered

statistically significant. All p-values were two tailed.

duration of surgery and (Table 1) and preoperative vitals (Table 2).

Results

There was no significant difference with respect to age, gender, weight and ASA physical status,

| Table 1. demographic characteristic of patients, operative data in studied groups (mean±SD)				
Variable	Group R	Group RT	Group RD	P Value
Age (years)	42.14	38.90	37.80	0.235
Gender male %	24.3	26.8	26.7	
female %	75.7	73.2	73.3	0.961
Weight (kgs)	64.7	62.7	63.5	0.682
ASA status ASA I (%)	78.4	82.9	86.7	0.611
ASA II (%)	21.6	17.1	13.3	
Mean duration with Range of surgery (min)	45.1 (28-56)	48.8 (32-59)	47.1 (28-59)	0.056

Table 2: Showing operative vitals of study patients among various groups					
Variables		Group R	Group RT	Group RD	P Value
Pre operative	HR	75.49	74.71	75.62	0.431
	Systolic BP	119.84	119.17	119.47	0.587
	Diastolic BP	76.24	77.05	77.09	0.476
	SPO2 (%)	97.73	97.95	98.04	0.367

Visual analogue scale at different time intervals over 24 hrs postoperatively were statistically significantly lower at all times in Group RD than Group RT and Group R (Table 3). Furthermore, overall VAS in 24 hrs was also significantly lower in Group RD (1.61 ± 0.292) than Group RT (2.65 ± 0.275) and Group R (3.94 ± 0.329)(Table 4). All these results had p value <0.001.
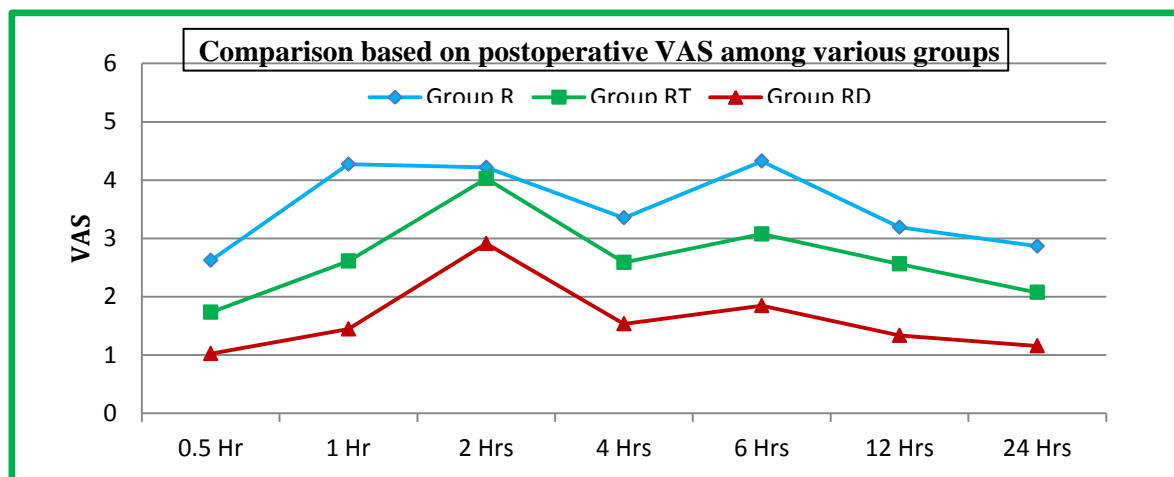

Table 4. Post operative overall vas score and total dose of analgesia consumed over 24 hrs.				
Variable	Group R	Group RT	Group RD	P-Value
Overall VAS (24 hrs)	3.94±0.329	2.65± 0.275	1.61± 0.292	<0.001
Total dose of diclofenac (rescue analgesia) in 24 hrs	140.60±23.83	109.80± 37.86	81.70± 21.59	<0.001

Total diclofenac consumption was also lowest in Group RD (81.70± 21.59 mg) than Group RT (109.80 ± 37.86 mg) and Group R (140.60 ± 23.83 min) (Table 4). The results were statistically significant with p value <0.001.

Showing 24 hour sedation score in various groups
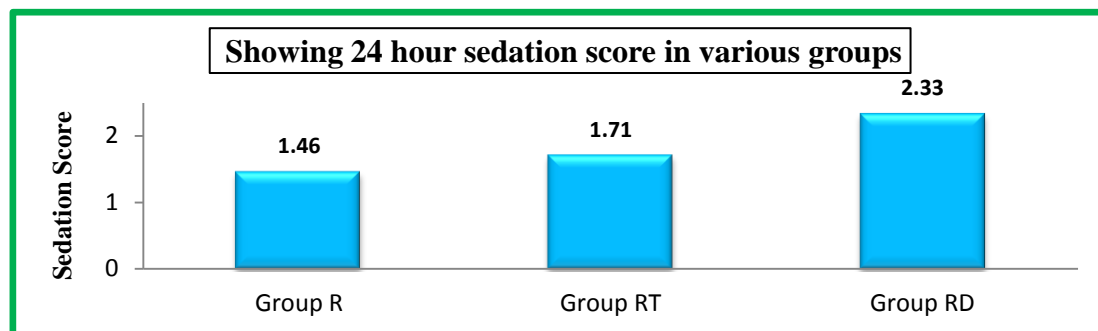
Time to first request of analgesia was longest in Group RD (141.8±14.75 min, range 81-244 minutes) as compared to RT (116.9±23.12 min, range 45-181 min) and Group R (63.7±11.97 min, range 32-130 min). The statistical difference was significant among the study groups (p<0.001) (Table 5).

Table 5. Time to first request of analgesia in postoperative period

Time (Minutes)	Mean± SD	Range (min)	P-value
Group R	63.7 ± 11.97	32-130	<0.001
Group RT	116.9 ± 23.12	45-181	<0.001
Group RD	141.8 ± 14.75	81-244	<0.001

Overall analysis showed that adverse events were not statistically significantly different in all the three study groups (*P* >0.05).

Showing postoperative complications among various groups
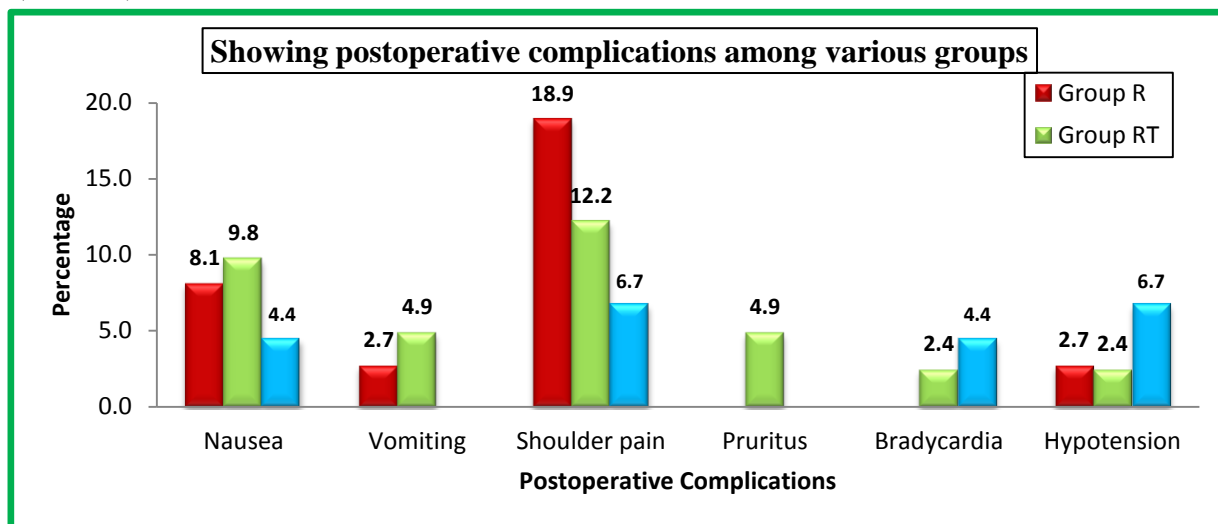
Discussion

The rationale for intraperitoneal administration of drugs for the treatment of the pain that follows laparoscopic surgery is that the small incisions at the abdominal wall cause visceral component of the pain and shoulder pain. With this in mind, many authors have tried to diminish pain via the peritoneal route. Intraperitoneal local anaesthetic is likely to blockade free afferent nerve endings in peritoneum. Systemic absorption of local anaesthetic from the peritoneal cavity may also play a part in reduced nociception although this would be expected to occur after any local anaesthetic technique.[16]

Mean duration of post-operative duration of analgesia in our study significantly longer in

Group RD than Group RT and group R which was found to be statistically significant (P<0.05).Our results correlated to results of U.Shukla, *et al.*[17] who also noted that the time to first request of analgesia in post operative period was significantly delayed in Group bupivacaine+dexmedetomidine (128±20 min) as compared to Group bupivacaine only (55±18 min) but was comparable to group that received bupivacaine with tramadol (118±22min) (*P* = 0.000). Our study was also in correlation with study done by Beder El Baz MM, Farahat TE et al[18] who found that first time for taking diclofenac was significantly lower in Group levobupivacaine + dexmedetomidine compared to Group levobupivacaine (*P* < 0.001) and Group normal saline (*P* = 0.025). Similar to our studyMemis*et al.*[19] also concluded that combination of tramadol or clonidine with intraperitoneal bupivacaine to be more effective than bupivacaine alone.

In our study Over all VAS score over 24 hrs also showed statistically significant difference (p<0.05) with group RD having least mean VAS compared to other two groups.Our results were consistent with results ofUshaShukla, T Prabhakar et al[17] also noted that VAS at different time intervals were statistically significantly lower at all times in Group Bupivacaine + Dexmedetomidine than Group Bupivacaine + Tramadol and Group Bupivacaine. Similar findings were also observed in study by Beder El Baz MM, Farahat TE et al[18] and Bakhamees et al.[20]

Our study showed total analgesia consumption of injection Diclofenac in 24 hours postoperatively was least in group RD followed by RT group and highest requirement was in R group with 81.70 mg, 109.80mg and 140.60mg, respectively.Similar results were also obtained by Singh A, Mathur SKet al[21] who showed that requirement of rescue analgesia (diclofenac) was lowest in patients receiving fentanyl with ropivacaine (84 ± 25 mg) as compared to ropivacaine alone(97 ± 47 mg) or normal saline(149 ± 42 mg) (p < 0.001). Our results also coorelated with results of Ahmed et

al[22] and Similar findings were also observed by Beder El Baz MM, Farahat TE et al [18] where they found that higher amounts of rescue analgesia diclofenac was needed in patients who received normal saline (203.5±42.9 mg) as compared to those who received levobupivacaine (117.8±63.7 mg) or those who received levobupivacaine + dexmedetomidine (46.3±41.3 mg) and the difference was statistically significant (*P* < 0.001). There were only few incidence of side effects encountered in our study like, nausea in 3,4 and 2 cases in Group R, RT and RD, respectively(p 0.88). Vomiting in 1, 2 and none case in Group R, RT and RD (p value 0.66). Shoulder pain in 7, 5, and 3 cases in group R, RT and RD, respectively (p 0.90); and Pruritis in only 2 cases in Group RT (p 0.40). Bradycardia in 1 and 3 pts in group RT and RD respectively and none in group R (p 0.79).Hypotension in 1, 1 and 4 cases in group R, RT and RD, respectively (p 0.83). Similar to our study, SrinivasRapolu, K Anil Kumar etal[23] found the incidence of shoulder pain significantly low in group Bupivacaine+Dexmedetomidine compared to group Bupivacaine. Similarly Singh A, Mathur SK et al[21] found emesis was highest in patients receiving normal saline group(18%) and same in patients receiving ropivicaine alone and with fentanyl (6% each). The difference being statistically insignificant (p = 0.069).Similarly findings were also observed by Beder El Baz MM, Farahat TE et al.[18]

Conclusion

Intraperitoneal instillation of local anesthetic is an easy, cheap and noninvasive method that provides good analgesia in the immediate postoperative period after laparoscopic cholecystectomy. Intraperitoneal Ropivacaine with Dexmedetomidine or Tramadol produces postoperative analgesia better than what was obtained with intraperitoneal ropivacaine alone. The combination of intraperitoneal Ropivacaine and Dexmedetomidine or Tramadol is superior to plain Ropivacaine for reducing postoperative pain in patients who underwent laparoscopic

cholecystectomy, without any significant increase in adverse events. Ropivacaine with Dexmedetomidine or Tramadol reduces not only the intensity of pain but also the total dose of rescue analgesic consumption.

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