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A COMPARATIVE STUDY OF INTRAPERITONEAL INSTILLATION OF 0.5 % ROPIVACAINE (PLAIN) VERSUS 0.75% ROPIVACAINE (PLAIN) IN REDUCING POST OPERATIVE PAIN AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

Aim: To compare post-operative anaesthetic effect of intraperitoneal 0.5% ropivacaine (plain) with intraperitoneal 0.75% ropivacaine (plain) in laparoscopic cholecystectomies. **Materials & Methods:** The present prospective double blinded randomized controlled trial was done on 120 patients of ASA 1 and 2 category of either gender between 18-70 years of age undergoing laparoscopic cholecystectomy at Department of Anaesthesia, Government Medical College And Rajindra Hospital, Patiala. The patients were randomized into three groups i.e. group A (received intra-peritoneal instillation of 20 ml 0.5% ropivacaine (plain) and 10 ml normal saline, group B (received intra-peritoneal instillation of 20 ml of 0.75% ropivacaine (plain) and 10 ml normal saline) and group C (received intra-peritoneal instillation of 30 ml of Normal Saline). The post operative pain was monitored using visual analogue score (VAS) at 1, 2, 4, 6, 12 hours after surgery and overall visual analogue score (mean of all VAS scores). Along with the VAS score, the hemodynamic parameters like heart rate, blood pressure, saturation was also recorded at the same time intervals. **Results:** All the hemodynamic variables viz. SBP, DBP, MAP and heart rate was found to be comparable among the study groups. Mean VAS was lower in group B and group A than in group C at all the time intervals. Duration of analgesia (hrs) was longer with Group B (5.31±1.28), as compared to Group A (3.89±1.07) and control group (1.09±0.26). **Conclusion:** Intra-peritoneal instillation of 0.75% Ropivacaine provides superior and prolonged pain relief without any adverse effects, making its use simple safe and effective for postoperative analgesia in laparoscopic cholecystectomy.

INTRODUCTION

Laparoscopic Cholecystectomy (LC) is the treatment of choice in treating gallbladder disease substituting the conventional Open method of Cholecystectomy (OC). LC has improved surgical outcome in terms of reduced pain, morbidity and duration of convalescence compared to open cholecystectomy but it is not a pain-free procedure, as many LC patients refrain from early recovery to normal activity which imperils the feasibility of LC as a low morbidity procedure[1]. There are three main sources for pain after laparoscopic cholecystectomy: the incision sites, the pneumoperitoneum [due to (a) local changes (peritoneal and diaphragmatic stretching) and (b) systemic changes (exaggeration of the local tissue inflammatory response)], and the gall bladder surgical bed in the liver after cholecystectomy. Incisional site contributes for up to 70% of pain after laparoscopic cholecystectomy and therefore many studies have been conducted to deal with incisional site pain[3].

There are various modalities available for postoperative pain relief ranging from parenteral analgesia (NSAIDS and opioids), epidural analgesia, peripheral nerve blocks, incisional infiltration and intraperitoneal (IP) instillation using local anaesthetics. Prevention of transmission of nerve signals from the trauma site to the spinal cord and reduction of neurogenic local inflammation at the trauma site has been reported with the use of local anaesthetics. As large volumes are required in these techniques, ropivacaine, a newer amide, may be preferred due to less risk of cardiovascular toxicity and central nervous system side effects[1].

Several studies have evaluated doses of ropivacaine as large as 300-375 mg for inguinal hernia infiltration and intra-peritoneal injections but did not observe any clinical evidence of toxicity. Thus ropivacaine allows for larger potent doses than bupivacaine with lesser risk of toxicity.[20syn]

Among the various local anaesthetics (LA) techniques, IP use of LA has gained attention and various researches have been done to study its efficacy for post-operative analgesia. The rationale to use the IP route is that the peritoneum is exposed to block of visceral nociceptive conduction, thereby providing an additional mechanism of analgesia. Most of the previous studies have shown that local anaesthetic with or without opioids can provide post-operative pain relief when instilled intraperitoneally. However scarce literature was reported evaluating the effect of ropivacaine administered intraperitoneally for post-operative analgesia following laparoscopic cholecystectomy[11]. Hence the present study was conducted to compare post-operative anaesthetic effect of intraperitoneal 0.5% ropivacaine (plain) with intraperitoneal 0.75% ropivacaine (plain) in laparoscopic cholecystectomies.

The objectives of the study are as follows:

a. To compare post operative anaesthetic effect of intraperitoneal 0.5% ropivacaine (plain) with intraperitoneal 0.75% ropivacaine (plain) as compared to the control group in laparoscopic cholecystectomies.

b. To evaluate the side effects of intraperitoneal 0.5% ropivacaine (plain) and 0.75% ropivacaine (plain) in laparoscopic cholecystectomies.

MATERIALS & METHODS

The present prospective double blinded randomized controlled trial was done on 120 patients of ASA 1 and 2 category of either gender between 18-70 years of age undergoing laparoscopic cholecystectomy. The study was

conducted in Department of Anaesthesia, Government Medical College And Rajindra Hospital, Patiala.

Sample Size:
In a previous study conducted by Kim et al[21], the pain score was high in the control group and the fentanyl consumption (ug/hr) within 4 hours after completion of laparoscopic surgery was 33.20±8.42 as compared to 15.82±6.73 in the ropivacaine group. The sample size is calculated to be n=120, 40 in each group .The sample size is calculated by using the formula:

$n=(Z1-\alpha/2+Z1-\beta)2\ 2*\sigma2\ /(\mu1-\mu2)\ 2$,

where Z1-α/2=1.96, was standard normal deviation at type 1 error α=0.05, Z1-β=0.84 was standard normal deviation at type 2 error β=0.20, σ was pooled standard deviation, μ1 and μ2 were the means in both the groups.

Inclusion Criteria
1. ASA class I and II
2. 18-70 years of age
3. Patients undergoing laparoscopic cholecystectomy.

Exclusion Criteria
1. ASA class III,IV,V and VI
2. Patients showing hypersensitivity to study drug
3. Patients having impaired liver and renal function
4. Patients having history of AV block, bradycardia, sick sinus syndrome, arrhythmias
5. Patients having history of seizures.

Pre-Anaesthetic Checkup
Pre-anaesthetic checkup was done for all patients under study, during which routine investigations, general physical and systemic examinations were done. The nature of study was explained to the patient and informed consent was taken in patient's vernacular language.

Premedication
All patients were kept nil per orally for a minimum of 6 hours prior to surgery for solids, 4 hours prior to surgery for clear fluids. Patients will be pre-medicated with Tab Etizolam 0.25 mg in the night before surgery.

Study Groups
The patients were randomized into three groups i.e. group A, B and C of 40 patients each. Randomization was done using sealed envelope system.
1. Group A received intra-peritoneal instillation of 20 ml 0.5% ropivacaine (plain) and 10 ml normal saline (30 ml total).
2. Group B received intra-peritoneal instillation of 20 ml of 0.75% ropivacaine (plain) and 10 ml normal saline (30 ml total).
3. Group C received intra-peritoneal instillation of 30 ml of Normal Saline (Control group).

Anaesthesia Technique
For all patients, once inside the operation theatre, continuous electrocardiogram, heart rate, oxygen saturation, and intermittent blood pressure monitoring was done. A running intravenous line was started. All patients were given Inj. Midazolam 2 mg i.v. for amnesia and Inj. Butarphenol 1 mg for intra- operative pain relief. In all patients, anaesthesia was induced using Inj. Propofol (1.5-2.5 mg/kg). They were given Inj. Vecuronium (0.08 to 0.1 mg/kg) for intubation and muscle relaxation. Anaesthesia was maintained using isoflurane along with oxygen and nitrous oxide.

At the end of the surgery, before ports were removed, 30 ml of drug mixture containing Inj. 0.5% ropivacaine or Inj. 0.75% ropivacaine was instilled using 3 ports into the peritoneal space. The hemodynamic parameters of all the patients were recorded at time of instillation of drug which was taken as baseline (0 minutes). The contents of the drug mixture were not known to the investigator, as the person preparing the drug mixture was not part of the study. The residual neuromuscular blockade at the end of the surgery will be reversed using Inj. neostigmine (0.05mg/kg) and Inj. glycopyrrolate (0.01 mg/kg).

The post operative pain was monitored using visual analogue score (VAS) at 1, 2, 4, 6, 12 hours after surgery and overall visual analogue score (mean of all VAS scores). Along with the VAS score, the hemodynamic parameters like heart rate, blood pressure, saturation was also recorded at the same time intervals.

Patients who reported VAS 3 or >3 were given Inj. Tramadol (2 mg/kg dose) as rescue analgesia. Patients were also observed for post operative nausea and vomiting. Patients who suffer from nausea and vomiting was given Inj Ondansetron 4 mg in 100 ml normal saline infusion. For all the patients, time to first request of rescue analgesia (considering time of drug instillation as 0), total dose of analgesia and side effects over 12 hours post operatively was noted.

Data was collected and subjected to statistical analysis.

Statistical Analysis
Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 25.00 for windows; SPSS inc, Chicago, USA). For each assessment point, data were statistically analyzed using one way ANOVA. Difference between two groups was determined using t test as well as chi square test and the level of significance was set at $p<0.05$.

RESULTS
Females were comparatively more as compared to males in all the study groups. Mean age in group A, B and C was 35.46±11.23, 34.61±10.49 and 35.19±10.37years in A, B and C group respectively. More than 2/3rd of the subjects had ASA grade I. All the baseline factors were comparable among the study groups as $p>0.05$ (table 1).

Table 1: Demographic Profile Among The Study Groups

Variables	Group A		Group B		Group C		p value
	N=40	%	N=4	%	N=40	%	
Gender							
Male	8	20	6	15	11	27.5	0.78
Female	32	80	34	85	29	72.5	
Age in years (Mean±SD)	35.46±11.23		34.61±10.49		35.19±10.37		0.81
ASA Grade							
Grade I	35	77.5	36	90	39	97.5	0.67
Grade II	5	22.5	4	10	1	2.5	
Weight in kg (Mean±SD)	62.74±10.30		61.91±9.53		60.28±10.55		0.59
Height in cm (Mean±SD)	162.05±11.21		160.14±11.43		164.5±10.18		0.73
Duration of Surgery (Mean±SD)	47.41±6.62		51.83±7.80		49.03±6.97		0.62

λ: anova test, $\chi2$: Chi square test

Mean MAP increases in both the groups after 5 and 10 minutes of block and then it decreased till 40 minutes. After 40 minutes of block, MAP was found to be increasing and in appropriate range. MAP was found to be comparable among the study groups at all the intervals as $p>0.05$ (table 2).

Table 2: Comparison Of MAP (Mean Arterial pressure) Among The Groups At Different Intervals

Interval	Group A		Group B		Group C		p value
	Mean	SD	Mean	SD	Mean	SD	
Baseline	95.73	6.55	96.69	7.73	98.71	9.75	0.18
5 min	106.04	6.42	100.83	8.22	102.85	10.24	0.29
10 min	101.15	6.74	95.98	7.93	98	9.95	0.24
15 min	97.88	6.53	92.59	9.25	94.61	11.27	0.33
20 min	93.55	7.18	90.02	8.79	92.04	10.81	0.2
30 min	89.37	7.44	85.83	12.08	87.85	14.1	0.1
40 min	81.26	7.84	78.19	7.87	80.21	9.89	0.58
60 min	94.87	7.13	91.48	7.01	93.5	9.03	0.75

Mean heart rate was found to be in appropriate range and comparable among the study groups at all the intervals as p>0.05 (table 3).

Table 3: Comparison Of Heart Rate Among The Groups At Different Intervals

Interval	Group A		Group B		Group C		p value
	Mean	SD	Mean	SD	Mean	SD	
Baseline	81.66	8.43	83.67	9.71	83.08	8	0.58
5 min	90.19	9.78	86.77	10.33	91.50	9.35	0.16
10 min	85.19	10.52	82.32	10.96	86.55	10.09	0.61
15 min	82.72	10.07	79.11	12.11	84.17	9.64	0.89
20 min	79.26	10.59	74.05	11.2	80.62	10.16	0.32
30 min	76.46	10.74	70.57	11.82	77.86	10.31	0.79
40 min	75.92	10.65	71.12	10.2	77.31	10.22	0.77
60 min	82.09	8.46	84.79	8.88	83.58	8.03	0.49

Mean VAS was lower in group B and group A than in group C at all the time intervals. The difference between Group C and A as well as B was statistically significant at 4 hour, at 6 hour, 12 hr, 24 hr and 48 hour (p value<0.05). Although VAS score was less in group B as compared to group A at all the intervals, but no significant difference was found (table 4).

Table 4: VAS Score Among The Study Groups

VAS	Group A		Group B		Group C		p value
	Mean	SD	Mean	SD	Mean	SD	
30 min	2.67	1.34	2.59	1.13	3.03	1.01	0.31
1 hr	2.88	1.07	2.81	1.35	2.97	1.22	0.54
2 hr	2.95	1.01	2.90	1.1	3.16	1.65	0.67
4 hr	2.66	1.01	2.59	1.1	3.05	1.08	0.039*
6 hr	2.5	0.96	2.42	0.87	3.01	1.05	0.016*
12 hr	2.43	1.35	2.33	0.98	3.14	1.32	0.028*
24 hr	2.61	1.14	2.40	1.02	3.02	1.01	0.011*
48 hr	0.52	1.08	0.26	1.17	2.25	0.96	0.005*

*: statistically significant

Duration of analgesia (hrs) was longer with Group B (5.31±1.28), as compared to Group A (3.89±1.07) and control group (1.09±0.26) and the difference among the groups was statistically significant. Total analgesic consumption was lesser with Group b (1±0.45) as compared to Group A (1.13±0.57) and control group (2.3± 0.46) as shown in table 5.

Table 5: Duration Of Analgesia And Its Consumption Score Among The Study Groups

Variables	Group A		Group B		Group C		p value
	Mean	SD	Mean	SD	Mean	SD	
Duration of analgesia (in hrs)	3.89	1.07	5.31	1.28	1.09	0.26	<0.01*
Analgesia Consumption	1.11	0.33	1.02	0.4	2.35	0.38	0.007*

*: statistically significant

Side effects were reported more in group B as compared to group A, though no significant difference was found (table 6).

Table 6: Side Effects Among The Study Groups

Side effects	Group A		Group B		Group C		p value
	N	%	N	%	N	%	
Nausea and Vomiting	2	5	2	5	4	10	0.73
Hypotension	1	2.5	3	7.5	0	0	
Bradycardia	0	0	1	2.5	0	0	
Pruritus	1	2.5	2	5	1	2.5	

DISCUSSION

The use of local anaesthetics for post-operative pain relief after LC has become a popular technique as a component of multi modal approach of postoperative pain management.

In this study; females were comparatively more as compared to males in all the study groups. Mean age in group A, B and C was 35.46±11.23, 34.61±10.49 and 35.19±10.37years in A, B and C group respectively. All the baseline factors were comparable among the study groups as p>0.05. In a study by Ayman A. Kasem et al[3], J Ramesh et al[2], Monika Gupta et al[1] and Tae Han Kim et al[17], all showed that there were no significant differences in respect of age, sex, body mass index (BMI), ASA class, and also the operation time between the group. This is similar to the present study.

All the hemodynamic variables viz. SBP, DBP, MAP and heart rate was found to be comparable among the study groups in this study. Monika Gupta et al[1], Shazia Shafi et al[15] and Tae Han Kim et al[17] in their study similarly revealed that hemodynamic variables were found to be comparable among the study groups at all the intervals as p>0.05.

Intraperitoneal LA is likely to block free afferent nerve endings in the peritoneum. Systemic absorption of local anaesthetic from the peritoneal cavity also play a part in reducing visceral pain. In the present study; mean VAS was lower in group B and group A than in group C at all the time intervals. The difference between Group C and A as well as B was statistically significant at 4 hour, at 6 hour, 12 hr, 24 hr and 48 hour (p value<0.05). Although VAS score was less in group B as compared to group A at all the intervals, but no significant difference was found. Kanta Bhati et al[5] in their study similarly revealed that VAS was lower with 0.75% ropivacaine, as compared to 0.5% ropivacaine and control group. Acharya et al found similar observations to our study that VAS scores are lower at all the time intervals in 0.75% ropivacaine.

Duration of analgesia (hrs) was longer with Group B (5.31±1.28), as compared to Group A (3.89±1.07) and control group (1.09±0.26) and the difference among the groups was statistically significant in this study. Meena RK et al found that mean duration of analgesia with intraperitoneal instillation of 0.75% ropivacaine (2mg/kg) was longer. In a study by Kanta Bhati et al[5], duration of analgesia (hrs) was longer with 0.75% ropivacaine as compared to 0.5% ropivacaine and control group. These findings are similar to the present study.

In the present study; total analgesic consumption was lesser with Group b (1±0.45) as compared to Group A (1.13±0.57) and control group (2.3± 0.46). These findings are similar to the study conducted by Kanta Bhati et al[5] i.e. total analgesic consumption in 12 and 24 hours was lesser with 0.75% ropivacaine as compared to 0.5% ropivacaine and control group. Sunil Chiruvella et al in their study reported similar findings too. A Singh et al11 found similar observation to our study that Intraperitoneal instillation of ropivacaine (0.75%) with fentanyl reduces not only the intensity of visceral, parietal and shoulder pain but also the total rescue analgesic dose consumption. Dinesh Singh, et al observed similar results to our study that intraperitoneal instillation of ropivacaine (0.5%) provides good analgesia in the immediate postoperative period after laparoscopic surgery.

Higher incidence of emetic symptoms in control group could be due to higher pain scores and thus greater autonomic response. Similar findings were obtained by Kucuk et al and Kanta Bhati et al[5].

Limitations Of Study

1) Pain is a subjective sensation and thorough objective

observation of such is difficult.
2) Total analgesic consumption could have been ascertained more precisely if the study were conducted for longer periods and sample size was large.

CONCLUSION

Intra-peritoneal instillation of 0.75% Ropivacaine provides superior and prolonged pain relief without any adverse effects, making its use simple safe and effective for postoperative analgesia in laparoscopic cholecystectomy.