Analgesics by Intraperitoneal Instillation for Laparoscopic Cholecystectomy: Efficacy Comparison between Ropivacaine and Bupivacaine

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ABSTRACT

Background and Aim: Postoperative pain relief following Laparoscopic cholecystectomy is a major concern as it may affect functional outcome. The present study was conducted to compare the analgesic efficacy of ropivacaine and bupivacaine as an intraperitoneal Instillation during laparoscopic cholecystectomy under general anaesthesia and during the post-operative period.

Material and Methods: Sixty patients were allocated meeting the necessary criteria were divided equally into two groups (30 per group) to receive either 20 ml 0.5% ropivacaine (Group A) or 0.5% bupivacaine (Group B) Instillation intraperitoneally at the end of surgery. The patients were given rescue analgesia when visual analogue scale (VAS) was more than or equal to 4 and/or visual rating scale (VRS) was more than or equal to 3. The primary objective was to compare VAS and VRS and rescue analgesic requirement. Secondary objectives were to assess post-operative adverse effects and complication if any.

Results: The mean VAS score and VRS score were comparable in both groups. Bupivacaine provides a slightly longer duration of analgesia and on other had Ropivacaine has higher safety profile at higher doses. Both have similar rescue analgesic doses and in systemic safety profile at this concentration.

Conclusion: Bupivacaine or ropivacaine in equal volume and concentration instilled intraperitoneally at the end of surgery in patients undergoing laparoscopic cholecystectomy shows comparable efficacy in relieving post laparoscopy pain especially in early postoperative hours.

Key Words: Intraperitoneal Instillation, Visual analogue scale, Visual rating scale, Ropivacaine, Bupivacaine

INTRODUCTION

Laparoscopic cholecystectomy as opposed to open cholecystectomy is currently the most accepted surgical technique for cholelithiasis.¹ Laparoscopic procedure has many advantages over open procedure such as less haemorrhage, better cosmetic results, lesser post-operative pain, and shorter recovery time leading to the shorter hospital stay and less expenditure. Although the pain following laparoscopic cholecystectomy is less intense than open surgery, patients often suffer visceral pain with coughing, respiratory movements and mobilization and shoulder tip pain secondary to peritoneal insufflations. The creation of pneumoperitoneum increases the intraabdominal pressure which shifts the diaphragm cephalad and reduces diaphragmatic excursions.

Leading to basal atelectasis, intrapulmonary shunting and ventilation-perfusion mismatch which can delay postoperative recovery and increase morbidity and costs. A direct and significant correlation between shoulder pain and delay in returning to normal daily activities has been reported.²

The complex humoral and neuronal response that occurs with surgery requires a balanced approach for perioperative pain management with minimal side effects from anaesthetic and analgesic drugs.³ The growing evidence suggests that treatment of postoperative pain should be preemptive, multimodal and opioid-sparing to accelerate recovery and avoid potential side effects. Intraperitoneal instillation of the local anaesthetic agent into gall bladder bed has been proved to be an effective method of postoperative analgesia in laparoscopic

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ISSN: 2231-2196 (Print)

ISSN: 0975-5241 (Online)

Received: 29.06.2020

Revised: 27.08.2020

Accepted: 28.09.2020

Published: 27.10.2020

cholecystectomy. It is an easy, non-invasive method associated with low pain scores and opioid consumption and less shoulder pain and emetic symptoms.⁴ There are many studies conducted to evaluate the analgesic potential of individual local anaesthetic agents like bupivacaine, ropivacaine, levobupivacaine as an intraperitoneal instillation. However, only a few studies are comparing the analgesic potential of two different local anaesthetics drugs.

In the present study, we compared the analgesic efficacy of two different local anaesthetic drugs, bupivacaine and ropivacaine as an intraperitoneal Instillation to provide adequate postoperative analgesia in patients undergoing laparoscopic cholecystectomy under general anaesthesia.

MATERIALS AND METHODS

This prospective, randomized, clinical study was conducted in 60 adult patients in the year 2012-2013. The study was approved by an institutional review board (IRB) (Letter no. ECR/138/Inst/2013) and informed written consent was obtained from all patients.

Patients selection, grouping and treatment schedule

Patients who were meeting the necessary inclusion criteria were divided equally into two groups of 30 each by computer-generated randomization. The sample size of 30 per group was selected on the presumption that most variables generally have normal distribution at a sample size of 30. This is based on the central limit theorem. As per the American Society of Anaesthesiologist (ASA) physical status 1 and 2 of disease were scheduled for laparoscopic cholecystectomy under general anaesthesia. Patients selected were in the age range of 18 to 65 years and patients of either sex were selected in the study. Patients with allergic to local anaesthetics, ASA III, ASA IV, pregnant women, those whose pain evaluation was judged unreliable because of neurological disease or treatment with steroids, NSAIDs or opioids before surgery and if any complication occurs during surgery or converted to open cholecystectomy were excluded. While one group of patients receive 20 ml 0.5% Ropivacaine (Group A), others receive 0.5% bupivacaine (Group B) Instillation intraperitoneally at the end of surgery. The anesthesiologist was blind to patient group assignment. Drugs were filled in a 20 ml syringe by an anesthesiologist not involved in the study. Study data were recorded by an observer blind to the treatment schedule on a predesigned Performa (Annexure I).

Preparation for surgery

In the operation theatre, standard anaesthesia monitors-pulse oximeter, cardio scope, NIBP were attached to the patient and baseline parameters such as pulse rate, blood pressure, SPO₂

were noted. An IV line was secured with 18/20 G IV cannula. Patients were premedicated with intravenous glycopyrrolate (0.2 mg/kg) and intravenous ondansetron (4 mg/kg). All patients were given injection acetaminophen (Perfalgan) 1 g intravenous 15 mins before induction as a part of pre-emptive analgesia. Intravenous injection midazolam (0.03mg/kg) and fentanyl (0.002mg/kg) were given. Preoxygenation was done for 5 min following which induction was done with injection Propofol 2mg/kg. Injection Succinylcholine (1.5-2mg/kg) was given to facilitate laryngoscopy and endotracheal intubation. Following laryngoscopy, the airway was secured with an appropriately sized endotracheal tube. Injection Vecuronium was given for intraoperative neuromuscular blockade. Nasogastric tube of appropriate size was inserted. Anaesthesia was maintained with 60:40 of N₂O and O₂ with Isoflurane (0.2-1% dial flow concentration) using a closed circuit. Standard intraoperative monitoring with the cardio score, blood pressure, oxygen saturation (SPO₂), ETCO₂ was done. Ventilation was adjusted to maintain end-tidal carbon dioxide between 25-40 mm Hg. CO₂ insufflation rate was kept around 5 l/min. Intrabdominal pressure was maintained between 10-12 mm Hg.

Intraperitoneal instillation and post-operative care

After removal of Gallbladder and peritoneal wash, the patient was given 15°-20° Trendelenberg's position and the surgeon was given syringe filled with 20 ml 0.5%. Bupivacaine or 20 ml of 0.5% Ropivacaine according to randomization to instil the drug in gall bladder fossa through subcostal trocar under direct laparoscopic control. The solution was sprayed on the upper surface of the liver and on right subdiaphragmatic space, to allow it to diffuse into the hepato-diaphragmatic space, near and above the hepatoduodenal ligament and gall bladder fossa. Neuromuscular blockade was reversed adequately at the end of the surgery with Injection Glycopyrrolate 0.008 mg/kg and Inj. Neostigmine 0.05 mg/kg and after thorough oropharyngeal suction patients were extubated. Postoperatively patients were monitored for 24 hrs at an interval of 30 mins, 2, 6, 8, 12, 16, 24 hours for the vital parameters and assessed using Visual analogue scale (VAS) and Visual Rating Prince Henry Scale.

Assessment of Pain

Visual Analogue scale system: Patients were presented with 10 cm line, It is 10 cms with endpoints labelled 0 for no pain and 10 for worst possible pain patient can imagine. Patients were asked to mark a point on the line indicating the intensity of pain. The results were measured with a metric ruler and scored between 0 and 10 indicating the intensity of pain.

Visual Rating Prince Henry Scale: No pain on coughing (score = 0), Pain on coughing but not on deep breathing

(score 1), Pain on deep breathing (score 2), Pain at rest but light (score 3), Pain at rest severe (score 4).

Other indices were incidence of shoulder pain within 24 hours post-operatively and time of occurrence of it, first time at which rescue analgesia was required and the total number of doses required in the postoperative period, nausea, vomiting, bradycardia (heart rate <60/min), tachycardia (heart rate >100/min), hypotension (<20% of baseline value), excessive sedation. The patients were given rescue analgesia (Tramadol 1mg/kg, intravenous) when VAS was more than or equal to 4 and/or VRS was more than or equal to 3. For nausea, vomiting like conditions patients received ondansetron (0.08-0.1mg/kg, intravenous).

Statistical Analysis

The data obtained were subjected to statistical analysis to find out the significant difference between the groups. Student's Unpaired t-Test and Mann Whitney test (wherever applicable) was used for quantitative data and Chi-square test was used for qualitative data. The difference between the two groups was considered significant when the P-value was found to be less than 0.05.

RESULTS

In the present study, the demographic data of the patients in both the groups was comparable ($p > 0.05$) concerning age, weight, sex and ASA grading (Table 1-3). The mean VAS score (Figure 1A) and VRS score (Figure 1B) at 2, 6,

8, 12, 16, 24 hours were monitored. It was found that mean VAS remained statistically nonsignificant throughout the post-operative period except at 8 and 16 hrs. Mean VAS in group A (Ropivacaine) was 3.90 ± 0.84 and that in group B (Bupivacaine) was 3.33 ± 0.48 , it was significant ($P < 0.05$). Also, at 16 hours, mean VAS was 2.97 ± 0.76 in group A versus 2.50 ± 0.68 in group B ($P < 0.05$). VRS among both groups remained comparable throughout the post-operative period ($P > 0.05$) except at 8 and 16 hours. Mean VRS at 8 hrs in group A (Ropivacaine) was 2.53 ± 0.63 and for group B (Bupivacaine) it was 2.13 ± 0.63 with statistical significance of $P < 0.05$. Also, at 16 hours, mean VRS in group A was 2.40 ± 0.56 and group B it was found at 1.87 ± 0.35 . This showed statistical significance $P < 0.01$.

Time of 1st dose of rescue analgesia was 8.41 ± 0.53 hours in group A (Ropivacaine) and 9.35 ± 0.83 hours in group B (Bupivacaine), the difference was statistically significant at $P < 0.01$ (Table 4). The mean number of doses of rescue analgesia required in group A (Ropivacaine) was 2.33 ± 0.66 and in group B was 2.0 ± 0.59 this was not statistically significant ($P = 0.065$) (Table 5). Shoulder tip pain was seen in 26.7% of patients in group A (Ropivacaine) and 13.3% of patients in group B (Bupivacaine). Difference between the group was not statistically significant ($P = 0.197$) (Table 6). Emesis was noticed by 6 patients (20.0%) from group A (Ropivacaine) and 7 patients (23.3%) from group B (Bupivacaine) and the difference was not significant ($P = 0.754$). There was no incidence of the postoperative adverse event like tachycardia, bradycardia, hypotension, excessive sedation in any of the patients in both groups.

Table 1: Demographic profile of the patient

Study Parameter	Group A				Group B				Unpaired T test	P Value
	Mean	Std. Dev.	Median	IQR	Mean	Std. Dev.	Median	IQR		
Age	43.83	6.80	44.00	12.00	43.50	4.92	44.00	6.00	0.218	0.829
Weight	60.8	9.17	60	14.25	61.97	9.496	62	15	0.484	0.63

Table 2: Demographic profile of the patient

SEX		GROUP		Total
		Group A	Group B	
Male	Count	13	14	27
	Percent	43.30%	46.70%	45.00%
Female	Count	17	16	33
	Percent	56.70%	53.30%	55.00%

Table 3: Distribution of ASA grading among the study group

ASA grade		GROUP		Total
		Group A	Group B	
I	Count	16	15	31
	Percent	53.30%	50.00%	51.70%
II	Count	14	15	29
	Percent	46.70%	50.00%	48.30%

Figure 1: Comparison of VAS (A) and VRA (B) at various duration among the study group. * $P < 0.05$ between two groups suggest the statistical significance at 8 and 16 hrs only.

Table 4: Comparison of time of requirement of 1st dose of rescue analgesia

Study Parameter	GROUP A				GROUP B				P-Value
	Mean	Std. Dev	Median	IQR	Mean	Std. Dev	Median	IQR	
Rescue analgesia given (hours)	8.41	0.53	8.25	0.83	9.35	0.83	9.75	1.74	$P > 0.05$

Table 5: Comparison of no of doses of rescue analgesia required

No. of doses of rescue analgesia required		GROUP		Total
		A	B	
1	Count	2	5	7
	Percent	6.70%	16.70%	11.70%
2	Count	16	20	36
	Percent	53.30%	66.70%	60.00%
3	Count	12	5	17
	Percent	40.00%	16.70%	28.30%

Table 6: Comparison of shoulder tip pain among both groups

Shoulder tip pain		GROUP		Total
		A	B	
Yes	Count	8	4	12
	Percent	26.70%	13.30%	20.00%
No	Count	22	26	48
	Percent	73.30%	86.70%	80.00%

DISCUSSION

Laparoscopic cholecystectomy is the preferred surgical technique for uncomplicated cholecystectomy. Laparoscopic cholecystectomy is one of the most frequently performed elective general surgical operations. The establishment of laparoscopic cholecystectomy as an outpatient procedure^{5,6} has accentuated the clinical importance of reducing early postoperative pain and nausea. Pain and opioids both may induce nausea. Thus, improved postoperative pain treatment using opioid-sparing regimens⁷ may facilitate a high success rate of outpatient laparoscopic cholecystectomy. Although the pain following laparoscopic cholecystectomy is less intense than open surgery, patients often suffer visceral pain with coughing, respiratory movements and mobilization and shoulder pain secondary to peritoneal insufflation. Instillation of an intraperitoneal local anaesthetic to reduce postoperative pain has been studied through randomized trials for more than 10 years⁸.

Our prospective double-blind randomized study was to compare and evaluate the efficacy and safety of Ropivacaine compared to Bupivacaine for postoperative pain relief after instillation intraperitoneally through the cannula of the laparoscope in patients undergoing laparoscopic cholecystectomy under general anaesthesia.

Both groups were comparable concerning demographic variables (age, sex, weight), and ASA grading. Both the groups followed the same trend as regards to the haemodynamic parameters (Heart rate, blood pressure, oxygen saturation) which remained comparable throughout the post-operative period without statistical significance.

While comparing analgesic efficacy in our study, the VAS and VRS score was comparable. Both groups were comparable concerning pain scores at all intervals except at 8 and 16 hours where mean VAS at 8 hours in group A (Ropivacaine) was (3.90 ± 0.84) and in group B (Bupivacaine) was (3.33 ± 0.48). This was significant statistically ($P < 0.05$). Mean VAS at 16 hours in group A was (2.97 ± 0.76) and in the group, B was (2.50 ± 0.68), this being significant statistically ($P < 0.05$). Similarly, VRS in both groups was comparable throughout the post-operative period except at 8 and 16 hours. Mean VRS at 8 hours in group A was (2.53 ± 0.63) and in

the group, B was (2.13 ± 0.63), this was significant postoperatively ($P < 0.05$) and at 16 hours, mean VAS in group A was (2.40 ± 0.56) and in the group, B was (1.85 ± 0.85). This was significant statistically ($P < 0.01$). Lower VAS and VRS score were found with Bupivacaine plus adrenaline treatment group and the number of doses of rescue analgesia was also lower in the Bupivacaine group.⁹ Previously effectiveness of intraperitoneal instillation of bupivacaine (50mg vs 100mg) was reported in laparoscopic cholecystectomy wherein patients who received a low dose of drug experienced more pain than those who received the higher dose.¹⁰ Our results in support of previous studies suggest the usefulness and comparative effectiveness of these two drugs as an analgesic.

We found that both groups were comparable concerning VAS and VRS scores except at 8 and 16 hours and bupivacaine showed slightly longer-acting analgesia compared to Ropivacaine as shown by the time at which the first dose of rescue analgesia needed as compared, which was significant statistically. The mean total number of rescue analgesic doses in the form of Injection Tramadol 1mg/kg IV was in group A (Ropivacaine) in group B (Bupivacaine). This difference was not significant statistically. Timing of receiving the first dose of rescue analgesia was slightly shorter in group A (8.41 ± 0.53 hrs) than in group B (9.35 ± 0.83 hrs). This was statistically significant ($P < 0.05$). The number of doses of rescue analgesia required was the same for both drugs (2.33 ± 0.61 group A vs 2.00 ± 0.59 group B) which is not statistically significant level.

Incidence of shoulder pain, as well as nausea and vomiting, were similar in both groups. Both ropivacaine and bupivacaine showed similar systemic safety profile without any adverse events in the form of tachycardia, bradycardia, hypotension, excessive sedation. On comparison of 20 ml of 0.5% Ropivacaine and Bupivacaine as an intraperitoneal instillation in patients undergoing laparoscopic cholecystectomy, we infer that both have near similar efficacy in providing adequate analgesia especially in early (up to 6 hrs) post-operative hours. Similar results were also found in the previous study which compares the efficacy of two doses of intraperitoneal bupivacaine for pain relief after operative laparoscopy in gynaecology.¹¹ Bupivacaine provides a slightly longer duration of analgesia, both are equally effective in preventing post-operative shoulder tip pain and emetic symptoms, similar in the total number of rescue analgesic doses required and similar systemic safety profile at this concentration and volume.

The limitation of our study was that we couldn't measure plasma concentration of local anaesthetics administered intraperitoneally, thus we limited the total dose and volume to 100 mg and 20 ml respectively being given only intraperitoneally without infiltration to avoid toxic concentrations. We also couldn't use IV patient-controlled analgesia system due

to non-availability to assess the exact amount of opioid consumption in two groups which would have to delineate the analgesic efficacy of ropivacaine and bupivacaine in terms of the opioid-sparing effect more profoundly.

We recommend more studies comparing Ropivacaine and Bupivacaine given intraperitoneally in varied doses being conducted with a larger sample size. While considering safety profile of Ropivacaine, more studies can be conducted with as a part of multimodal analgesia to provide more profound and prolonged pain-free postoperative period in patients undergoing laparoscopic cholecystectomy and more studies can be conducted comparing Ropivacaine and Bupivacaine being administered intraperitoneally in combination with wound infiltration.

CONCLUSION

Bupivacaine or ropivacaine in equal volume and concentration instilled intraperitoneally at the end of surgery in patients undergoing laparoscopic cholecystectomy showed comparable efficacy in relieving various components of post laparoscopy pain (visceral, parietal, shoulder tip pain) especially in early postoperative hours. Bupivacaine provides a slightly longer duration of analgesia. Both Bupivacaine and Ropivacaine are similar in requirement of rescue analgesia doses and preventing emetic symptoms and had a similar safety profile.

ACKNOWLEDGMENT

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references to this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals, and books

from which the literature for this article has been reviewed and discussed.

Conflict of Interest: Nil

Source of Funding: Nil

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