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Original Research Article

Comparative Study of Intraperitoneal Infiltration of 0.5% Ropivacaine with and without Morphine in Laparoscopic Cholecystectomy for Post-Operative Analgesia

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Abstract:

Introduction: Patients after laparoscopic cholecystectomy complain more of visceral pain which results from the stretching of intra-abdominal cavity, peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity. Intraperitoneal (IP) local anaesthetics and opioids are gaining popularity for better pain relief in laparoscopic surgeries. The rationale to use the intraperitoneal route is that the peritoneum is exposed to blocking of visceral nociceptive conduction, thereby providing an additional mechanism of analgesia.

Methods: All eligible patients were randomly allocated into two groups as Group R (0.5% Ropivacaine group) and Group M (0.5% Ropivacaine plus Morphine group) by using calendar odd and even date method. At the end of surgery, after removal of gallbladder, study drug was instilled onto the gallbladder bed intraperitoneally via port under vision. Group R patients received 20ml of plain 0.5% ropivacaine while Group M received patient's received18ml of plain 0.5% ropivacaine plus 2ml (3mg) morphine. The main aim of our study was to assess the postoperative duration of analgesia in both the groups with NRS (Numerical Rating Scoring) and hemodynamic changes as respiratory rate, heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) after IP instillation of the study drug.

Results: In both groups, demographic profile were comparable and statistically insignificant. NRS scores was significant after a time interval of two hours postoperatively between the two groups, the difference remained up to 5 hours (p-value <0.05).In Group M, pain(NRS) score was significantly lower than the patients of ropivacaine 0.5% (Group R).The time of first rescue analgesia was statistically significantly longer in Group M(278±53.39 minutes)than Group R (216±49.03minutes)- (p value <0.0001). There was no statistically significant difference in haemodynamic parameters and mean respiratory Rate (p value >0.05) in the two groups.

Conclusion: The findings of the study demonstrate that patients receiving the combination of morphine and ropivacaine experienced a notably lower pain scores and extended time to the first rescue analgesia. This suggests a synergistic interaction between morphine, an opioid analgesic and ropivacaine, a local anaesthetic, resulting in enhanced and prolonged postoperative analgesia.

Keywords: Morphine; Ropivacaine; Cholecystectomy; intraperitoneal.

Introduction

Laparoscopic cholecystectomy is a commonly performed procedure for treating symptomatic gallstones [1]. The type of pain after laparoscopic surgery differs considerably from that seen after laparotomy [2,3]. Patients after laparoscopic cholecystectomy complain more of visceral pain which results from the stretching of intra-abdominal cavity [4], peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity [5,6]. As laparoscopic surgeries are gaining popularity, different modalities of perioperative pain management are being used. Enhanced recovery after surgery (ERAS) programmes aim at multimodal analgesic regimens to minimise postoperative opioid use and apart from the parenteral route of analgesic use, intraperitoneal (IP) local anaesthetics and opioids are gaining popularity for better pain relief in laparoscopic surgeries. [7] Different modalities have been proposed to relieve postoperative pain after laparoscopic surgeries, for example, non-steroidal

anti-inflammatory drugs (NSAIDS), opioids, IP local anaesthetics, intraperitoneal saline, removal of residual insufflation gas or gas drains, low-pressure abdominal insufflation, acetazolamide administration, use of nitrous oxide instead of carbon dioxide, and so on [8]. Injecting local anaesthetics through infra umbilical port on peritoneal bed and port site instillation of local anaesthetic has been used to reduce post-operative pain and decrease use of intravenous opioids [9]. The rationale to use the intraperitoneal route is that the peritoneum is exposed to blocking of visceral nociceptive conduction, thereby providing an additional mechanism of analgesia [3,8]. It is reported that intraperitoneal administration of ropivacaine combined with tramadol decreases postoperative pain and reduces analgesic requirements in patients undergoing laparoscopic cholecystectomy as compared to the use of ropivacaine alone [10]. Limited literature is available which compares IP ropivacaine with opioid for postoperative analgesia in laparoscopic surgeries.

Hence, this study was designed to compare the efficacy of 0.5% ropivacaine and 0.5% ropivacaine with morphine to provide postoperative analgesia after laparoscopic cholecystectomy.

Methods

This study was conducted in our institute for a period of 18 months after due approval from Institutional Ethical Committee. Written informed consent was taken from all the patients prior to study. The patients included in the study were educated about the standard NRS, i.e. pain is to be rated on a score of 0-10 (Zero for no pain; score of one, two and three for mild pain; four, five, six for moderate pain; seven, eight, nine and ten for severe pain).

The minimum required sample size for the study was calculated using Raosoft software for a comparative study. A total of 60 patients of ASA (American society of Anaesthesiologists) of physical status I & II and age group between 18-65 years, scheduled for laparoscopic cholecystectomy were selected for the study. Exclusion criteria included patients who denied consent, ASA grade III and above and surgeries converted from laparoscopic to open cholecystectomy. The main aim of our study was to assess the postoperative duration of analgesia in both the groups with NRS (Numerical Rating Scoring) and hemodynamic changes as respiratory rate, heart rate, systolic blood pressure (SBP)and diastolic blood pressure (DBP) after IP instillation of the study drug.

All eligible patients were randomly allocated into two groups as Group R (0.5%Ropivacaine group) and Group M (0.5%Ropivacaine plus Morphine group) by using calendar odd and even date method. Group M patients were allocated on even calendar dates while Group R were allocated on odd calendar dates. The preparation of the study drugs and its administration was done by different anaesthesiologists for both the groups who were blinded to the study drugs. After shifting the patient to the operating room on the day of surgery and securing an intravenous line, GE Avance CS2 19 inch display monitor was attached to the patient. Baseline values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR) and oxygen saturation (SPO_2) were recorded. General anaesthesia was induced with intravenous fentanyl 2mcg/kg, propofol 2mg/kg and vecuronium 0.1mg/kg while intraoperative anaesthesia was maintained with 1 to 1.5 MAC Isoflurane, 50% oxygen in air and positive pressure ventilation .For intraoperative analgesia, intravenous paracetamol 15mg/kg and fentanyl 25mcg intermittently was administered. At the end of the surgery after removal of gallbladder, study drug was instilled onto the gallbladder bed intraperitoneally via port under vision. Group R patients received 20ml of plain 0.5% ropivacaine while Group M received patient's received18ml of plain 0.5%ropivacaine plus 2ml (3mg) morphine. At the end of surgery, patient's trachea was extubated after reversal of neuromuscular blockade and then patient shifted to Post Anaesthesia Care Unit. After patient was fully awake, pain was assessed using NRS by another team member of Anaesthesiology. The NRS and hemodynamic parameters were recorded postoperatively at time intervals of 2, 5,10,15 and 30 minutes and thereafter hourly till the first requirement of rescue analgesia in the postoperative period. Rescue analgesia was given when NRS score= or > than 5(moderate pain) as 20mg/kg intravenous paracetamol and repeated 8 hourly or accordingly as per patient requirement. Side effects due to 0.5% ropivacaine and morphine such as nausea, vomiting, pruritis, sedation, respiratory depression and any other allergic reaction were observed and treated accordingly.

The primary data was collected in paper-based form. Thereafter, the data was entered in Microsoft Excel. The coded data was imported into Stata 17.1 version for analysis. For the continuous data, the author calculated the mean, median, mode, and standard deviation. For discrete data, the author calculated and reported frequency, proportion and percentage. Comparison of continuous variables with baseline values was analysed using a student's t-test in each group. Categorical variables were analysed using Chi-square test. We followed the scientific convection for detecting a significant difference between two groups of P-value < 0.05.

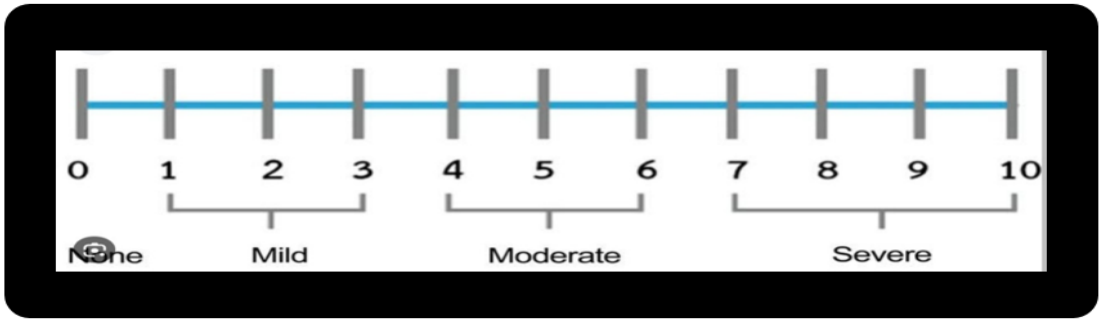

Figure 1: Numerical Rating Scale

Results: For the recruitment of 60 patients,72 patients were approached undergoing elective laparoscopic cholecystectomy out of which four patients refused to participate in the study and eight patients were excluded using the selection criteria .In both groups demographic profile was comparable and difference was insignificant(Table 1 & 2).

Table 1: The mean age groups for Group M (52.2) and Group R (48.9) are close, and the p-value of 0.4181 indicates that the difference is not statistically significant

Age group wise distribution of the patients (n =60)				
Age Group (in years)	**Group M (n=30)**		**Group R (n=30)**	
	n	**%**	**n**	**%**
18-30 Years	0	0.00	3	10.0
31-45 Years	11	36.67	6	20.00
46-60 Years	18	60.00	20	66.67
60- 80 Years	1	3.33	1	3.33
Mean Age (±SD)	**52.2 (±5.67)**		**48.9 (±6.21)**	
P- value = 0.4181				

Table 2: The difference between two groups is not statistically significant, as indicated by the p-value of 0.5839

Gender wise distribution of the patients (n =60)				
Gender	**Group M (n=30)**		**Group R (n=30)**	
	n	**%**	**n**	**%**
Female	19	63.33	21	70.0
Male	11	36.67	9	30.0
Pearson Chi2 = 0.30; P-value = 0.5839				

Table 3: Numerical Rating Scale between the two groups during the postoperative period

Numerical Rating Scale during the postoperative period (n=60)			
Time (in Minutes)	**Group**		**P-value**
	Group Morphine + Ropivacaine.	**Group Ropivacaine**	
	Median (NRS)	**Median (NRS)**	
Baseline	1	1	0.922
2 minutes	0	1	0.912
5 minutes	0	1	0.923
10 minutes	0	1	0.912
15 minutes	1	1	0.911
30 minutes	1	1	0.821
60 minutes	1.5	2	0.0779
120 minutes	2	3	0.0002*
180 minutes	2	4	<0.0001*
240 minutes	3	5	0.0001*
300 minutes	3	6	0.0092*
360 minutes	6	-	-
*- P-value statistically significant at these time points			

The observed NRS scores suggest significant difference in postoperative analgesia between the two groups. There was no significant difference in the NRS score up to 60 minutes of postoperative period. However, after a time interval of two hours, there was significant difference in the NRS scores between the two groups that lasted for up to 5 hours after surgery (p-value < 0.05). Patients given both morphine and 0.5% ropivacaine i.e., in group-M rated their pain (NRS) score significantly lower than patients given only 0.5% ropivacaine (group R).

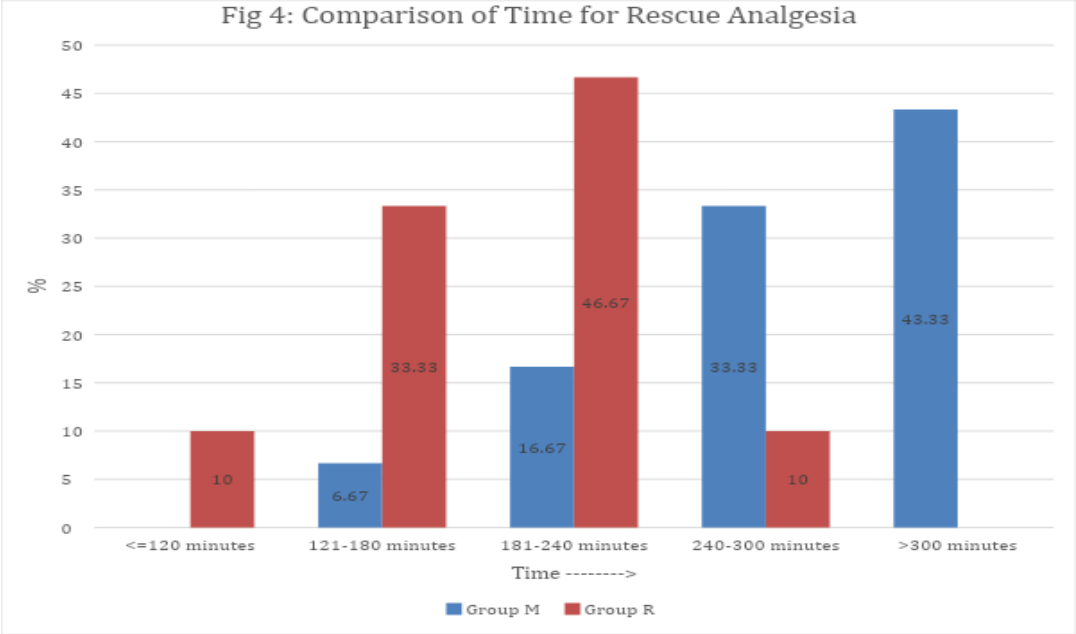

Figure 2: Comparison of Time of first rescue analgesia

Figure 2: illustrates that mean value to first rescue analgesia was highly significantly longer among patients in Group M (278 ± 53.39 minutes) than Group R (216 ± 49.03 minutes), as the p-value was < 0.0001, which is statistically highly significant. The respiratory rate is displayed as median values with their corresponding Interquartile Ranges (IQR). No significant differences were observed between the groups initially at baseline. However, at time intervals 5, 10, 15, 60 minutes, there was statistically significant differences in respiratory rate between the two groups (p <0.05) (Figure 3.).

As time progressed, the differences tended to diminish becoming statistically insignificant at later time intervals from 180 minutes onward.

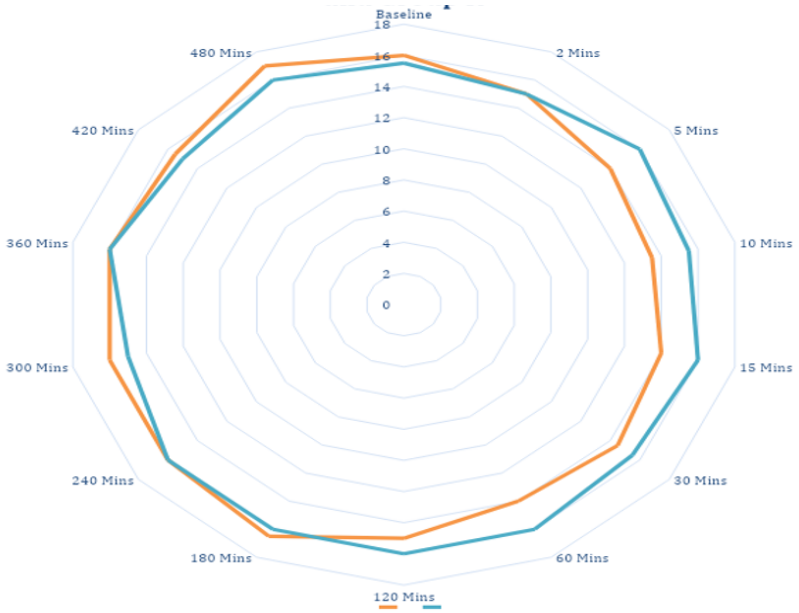

Figure 3: Comparison of respiratory rate in Group M and Group R

Throughout the time intervals, there was no statistically significant difference in mean systolic blood pressure between Group M and Group R. The mean systolic blood pressure values for both groups remained consistent and did not show significant variations. At some time intervals, such as 10, 30 and 420 minutes, there were trends indicating potential differences between the groups, but these differences were not statistically significant ($p > 0.05$).On the other hand, also the mean diastolic blood pressure values for both groups remained stable and did not show any significant variation between the groups. Comparison of side effects between Group M and Group R patients can be seen in table 4.Three patients (10%) in Group M experienced nausea and vomiting while there were no side effects noted among patients in Group R (0%). This difference was statistically insignificant with a P-value of 0.076. While one patient (3%) in Group M experienced pruritus (itching), none of the patients in either group experienced sedation, bradycardia or respiratory depression.

Table 4: Percentage distribution of side effects (n=60)

Side Effects	Group M (n=30)		Group R (n=30)		P-value
	n	%	n	%	
Nausea & vomiting	3	**10.00**	0	**0.0**	0.076
Pruritus	1	**3.0**	0	**0.0**	0.296
Sedation	0	**0.0**	0	**0.0**	-
Bradycardia	0	**0.0**	0	**0.0**	-
Respiratory depression	0	**0.0**	0	**0.0**	-
- Based on Chi-squared Test					

Discussion:

The observations of this study shows that the median NRS score during the first hour in the post-operative period in both the groups remained low and were comparable (p-value >0.05). After one hour, median NRS score in Group R was noted to be on the higher side as up to 5 at 240 minutes (04 hours) which was statistically significant ($p<0.05$) with Group M where the maximum median NRS score was noted at 360 minutes. Study by Butala BP et al. (2013) [11] compared the effectiveness of bupivacaine and morphine for alleviating postoperative pain following laparoscopic gynaecological surgeries. They too reported that during the first postoperative hour, the pain scores among the patients in the two groups were comparable.

Morphine when added as an adjuvant to local anaesthetic prolonged the duration of analgesia and also decreased the requirement of rescue analgesia. In Group M at 240 minutes, only 16% of patients required first rescue analgesia where as in Group R at this time interval 46.6% of patients were given first rescue analgesia and after 300 minutes, the difference between Group M (278 ±53.39)and Group R (216 ±39.03)was highly significant (p-value <0.0001).Kumari A et al., [9] in their study concluded that intraperitoneal administration of ropivacaine combined with tramadol resulted in less postoperative pain and reduced the need for rescue analgesics compared to ropivacaine alone in patients undergoing laparoscopic cholecystectomy. They observed a statistically significant difference in the average NRS scores between the two groups from 2.5 hours onwards that lasted up to 24 hours after surgery ($P < 0.05$).and also reported that fewer patients in the ropivacaine and tramadol group required rescue pain medication (42.5% vs 75%, P = 0.003) and less fentanyl as rescue analgesia overall (785 µg vs 1800 µg). These findings align with existing literature suggesting that combining opioids with local anaesthetics can result in prolonged and more effective pain relief following surgery. Studies have demonstrated the benefits of opioid adjuncts to local anaesthetics in various surgical procedures, highlighting their potential to enhance postoperative pain management.

Group R displayed fluctuations in their median respiratory rate over time. For instance, Group M exhibited a gradual decline in respiratory rate from baseline to the 480-minute interval, with statistically significant differences observed at several time points. Conversely, Group R maintained a more consistent respiratory rate across most time intervals, showing smaller fluctuations. The reduction in respiratory rate observed with the addition of morphine to ropivacaine aligns with the well-documented side effect profile of opioids, particularly respiratory depression as reported by Brook K et al., and Stein C et al., [12,13] in their respective studies.

In a clinical context, this finding underscores the importance of vigilant monitoring for respiratory depression when opioids like morphine are used in combination with local anaesthetics like ropivacaine, especially in postoperative settings as recommended by Deshler BJ et al., [14] in the context of multimodal analgesia .In our study there is no significant changes in blood pressure in both the groups throughout the time interval. Our study's findings align with findings of Rutherford D et al.,

(2021) [15] who conducted a meta-analysis of 13 studies and found that there was no difference in the rate of haemodynamic parameters including blood pressure values between those receiving local anaesthetic. Combined use of morphine and ropivacaine may increase the risk of these side effects. However, the difference between the two groups was statistically insignificant. More importantly, none of the patients in both the groups experienced any severe side effects, as respiratory depression, sedation, or bradycardia. Butala et al. (2013) [10] also supported our findings where four patients in the morphine and bupivacaine group and three patients in the bupivacaine only group reported nausea and vomiting. These collective findings suggest a general trend; while there might be a slight increase in certain side effects like nausea, vomiting, or itching when morphine is combined with local anaesthetics like ropivacaine or bupivacaine, the occurrences are not statistically significant. The limitations of our study was small sample size, conducted at single centre and short term follow up and limited outcome measurement.

Conclusion:

The results clearly indicate that the addition of morphine to ropivacaine significantly enhances the analgesic effect as evidenced by prolonged analgesia, delayed need for rescue analgesia and overall improved pain control compared to ropivacaine group.

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