

A Comparative study of intraperitoneal instillation of Bupivacaine (0.5%) and Ropivacaine (0.5%) for post-operative analgesia in Laparoscopic Cholecystectomy: A randomised controlled trial

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Abstract

Background: Many of the patients experience moderate to severe pain in the early post-operative period of laparoscopic cholecystectomy even though it is a minimally invasive procedure. To ameliorate this pain, multimodal approaches have been tried. To reduce post-operative pain and decrease the need for post-operative analgesics, intraperitoneal instillation of local

anaesthetics has been used in different doses and at different sites.

Objectives: This study aimed to compare the period of post-operative analgesia and evaluate the need of rescue analgesia in patients undergoing laparoscopic cholecystectomy, after intraperitoneal instillation of Bupivacaine and Ropivacaine in post-operative period.

Design: This was a prospective, randomised, double-blinded clinical study.

Setting: Tertiary care centre, conducted from December 2019 to June 2021.

Patients: 80 patients undergoing laparoscopic cholecystectomy.

Interventions: Random assignment of the patients was done to receive intraperitoneal instillation of Bupivacaine (0.5%) or Ropivacaine (0.5%) during the surgery.

Main outcome measures: Endpoint was time of first rescue analgesia with Inj. Diclofenac 75mg given intravenously if VAS>5 in post-operative period.

Results: In Ropivacaine group, heart rate was comparatively lower than Bupivacaine group, whereas a significantly lower Diastolic Blood Pressure (DBP) was present in Bupivacaine group at 6hour. The Ropivacaine group had a significantly lower VAS score. Time to first rescue analgesia need was also longer with Ropivacaine group, showing longer duration of analgesia in this group.

Conclusions: Post-operative pain relief is obtained by intraperitoneal instillation of local anaesthetic drug for patients undergoing laparoscopic cholecystectomy. Better analgesia was provided by intraperitoneal instillation of Ropivacaine (0.5%) when compared to intraperitoneal instillation of Bupivacaine (0.5%).

Trial registration: ctri.nic.in / identifier: CTRI / 2020 / 09/028020

Keywords: Laparoscopic Cholecystectomy, Intraperitoneal Instillation, Bupivacaine, Ropivacaine.

Introduction

Laparoscopy is one of the oldest GI endoscopic procedures. "Laparoscopy is defined as the telescopic visualisation of the abdominopelvic cavity through small incisions made on the abdominal wall with various instruments"¹. Many of the patients experience

moderate to severe pain in the early post-operative period even though the procedure is minimally invasive.

"Laparotomy results in parietal pain, whereas laparoscopy has a visceral component, a somatic component and shoulder pain secondary to diaphragmatic irritation as a result of CO₂ pneumoperitoneum², also by stretching of the abdominal wall during pneumoperitoneum and release of inflammatory mediators, local dissection and irritation of peritoneum produced by blood".

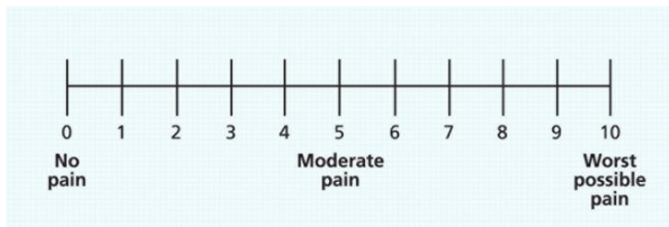
"Multimodal approaches have therefore been tried to ameliorate post-operative pain. These include parenteral analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs)³, local infiltration with local anaesthetics⁴ to lessen the overall pain and post-operative complications of patients undergoing laparoscopic surgeries"⁵. Also, at different sites and in different doses the use of intraperitoneal instillation of Bupivacaine and Ropivacaine has been used with varied success. There is a decrease in the need for rescue analgesia apart from being effective in the relief of post-operative pain.

A long-acting amide local anaesthetic, Bupivacaine, works by blocking the transmission of pain signals from the nerves to dorsal horn of the spinal cord, which helps decrease the sensation of pain, whereas Ropivacaine along acting amide local anaesthetic is formulated as the pure S-enantiomer. It is chemically related to Bupivacaine, but it has been shown to be less toxic to cardia and central nervous system compared to Bupivacaine"^{6,7}.

To quantify pain, specific pain assessment scales are used. This is a challenge however, because pain is a subjective experience that is influenced by psychological, social, cultural and other variables⁸.

There is availability of a number of different patient self-assessment scales.

The most commonly used method to assess pain is the Visual Analogue Scale (VAS) which was first described in 1966. There are two anchor points of 'no pain' and 'worst pain imaginable' on a 10 cm line which is self-assessed by the patient. The pain experienced by the subject is measured by the position of the mark on the line.



The purpose of this study was to compare the duration of post-operative analgesia and assess the need of rescue analgesia in patients undergoing laparoscopic cholecystectomy after intraperitoneal instillation of Bupivacaine and Ropivacaine in post-operative period.

Materials And Methods

After obtaining permission from institutional ethical committee, 80 patients who fulfilled the inclusion and exclusion criteria were taken up for the study.

Inclusion Criteria

1. Patients aged between 18-65 years.
2. American Society of Anaesthesiologist (ASA) physical status 1 and 2
3. Either gender
4. Weighing between 50-70 kg

Exclusion Criteria

1. Local anaesthetic hypersensitivity
2. Allergy to drugs used
3. Emergency laparoscopic cholecystectomy surgeries
4. Regular use of NSAIDs and analgesics
5. Uncontrolled systemic disorders

6. Pregnant and lactating females

Pre-operatively, each patient was visited, and a written informed consent was taken, after explaining the procedure. Pre-operative evaluation and all the required routine investigations for the proposed surgery were done. Absolute fasting for at least 8 hours was asked to be done by patients.

Patients were randomised using a computer-generated randomisation chart on entering the operating room.

Group B – 40 patients received 25ml of Bupivacaine (0.5%)

Group R – 40 patients received 25ml of Ropivacaine (0.5%)

After securing 18G IV cannula, standard ASA monitors which includes Pulse Rate (PR), Non-invasive Blood Pressure (NIBP), Electrocardiogram (ECG), measurements of end tidal gas were connected and base line parameters recorded.

Premedication with Inj. Glycopyrrolate 0.005mg/kg IV, Inj. Ondansetron 0.1mg/kg IV was done for the patients, 15 minutes prior to surgery and preoxygenated with 100% Oxygen for 3minutes. Inj. Propofol 2mg/kg IV was used for induction of anaesthesia, Inj. Fentanyl 2mcg/kg IV was given for analgesia; Inj. Atracurium 0.5mg/kg IV was used for relaxation and an appropriately sized cuffed endotracheal tube was used for intubation. Maintenance of anaesthesia was done with Oxygen: Nitrous Oxide (2:3), Sevoflurane (1-2%) and additional Atracurium was given as deemed necessary. All patients received Inj. Paracetamol 1g IV infusion intraoperatively.

The study drug of 25ml was instilled intraperitoneally- 10ml in the subdiaphragmatic area, 10ml in the gall bladder bed, 5ml in the omentum (the area of handling), through infraumbilical main port incision after the

removal of gall bladder and complete washing of peritoneal cavity and aspiration of solution used for irrigation, before removal of trocar and wound closure. The patient was kept in Trendelenburg position for 10 minutes, to facilitate dispersion of drug solution in the subhepatic region.

After return of spontaneous ventilation, residual neuromuscular blockade was reversed with Inj. Neostigmine 0.05mg/kg IV and Inj. Glycopyrrolate 0.01mg/kg IV, and endotracheal tube was removed.

Visual analogue scale for pain and haemodynamic changes were assessed serially at 0, 1, 2, 4, 6, 8, 12, 24 hours post-surgery. Rescue analgesia with Inj. Diclofenac 75mg IV was administered if VAS>5.

Recording of the total analgesic requirement was done in the first 24 hours.

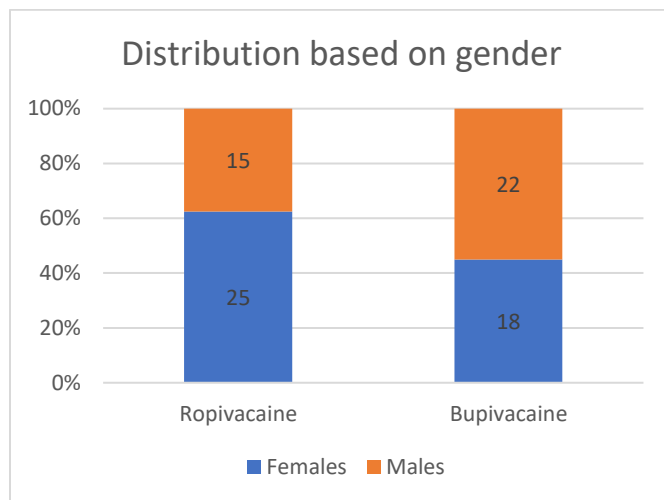
Statistical Analysis

SPSS software version 22 was used for analysis. Data is presented in suitable tabular and graphical forms, presented as proportion for qualitative data, mean and standard deviation for quantitative data. The test of significance for qualitative data (Gender, rescue analgesia, shoulder tip pain) was chi-square test and for quantitative data (Age, HR, SBP, DBP, MAP, SpO2, VAS) unpaired t-test was used. Statistical significance was set at P value <0.05.

Observations & Results

Table 1: Distribution of study participants based on gender

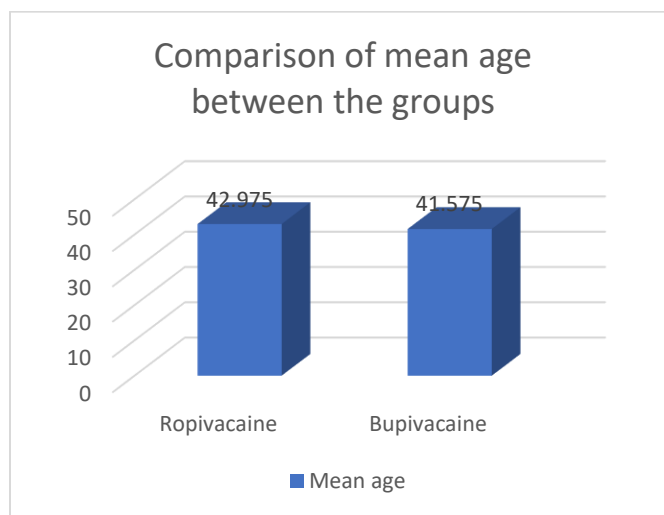
Gender	Ropivacaine		Bupivacaine		P value
	Frequency	Percentage	Frequency	Percentage	
Females	25	62.5%	18	45.0%	0.116
Males	15	37.5%	22	55.0%	
Total	40	100.0%	40	100.0%	



The difference in gender distribution is not statistically significant between the two groups.

Table 2: Distribution of study participants based on age

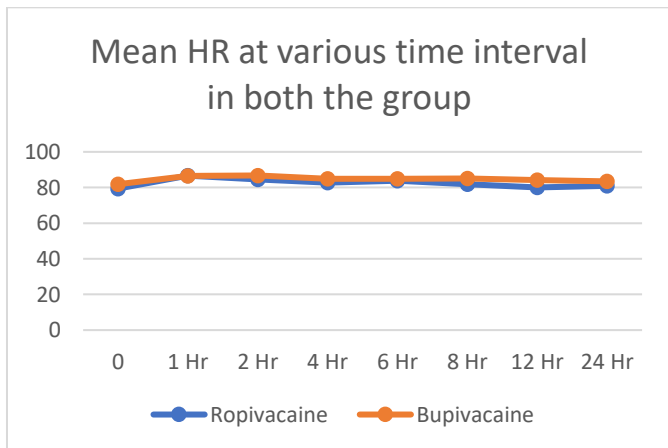
Groups	Age		P value
	Mean	SD	
Ropivacaine	42.975	9.4231	0.542
Bupivacaine	41.575	10.9822	Not significant



The difference in age between the two groups is not statistically significant.

Table 3: Comparison of heart rate among both the groups at various time interval

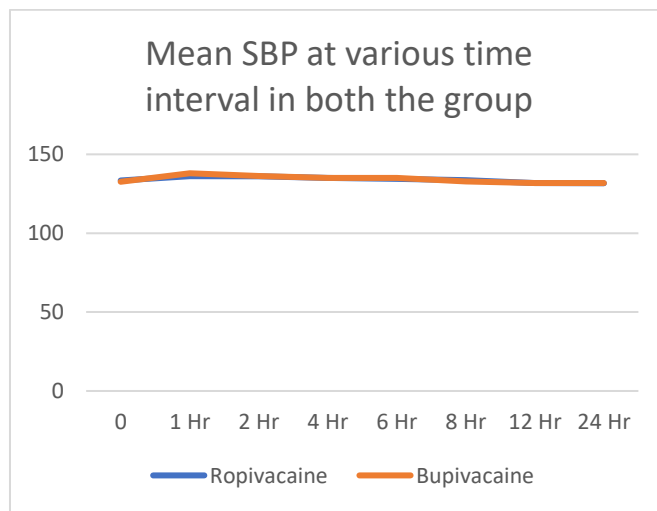
Heart rate at various time interval	Ropivacaine		Bupivacaine		P value
	Mean	SD	Mean	SD	
0	79.400	7.7420	81.850	7.3921	0.152
1 h	86.650	7.3504	86.500	6.6679	0.924
2 h	84.600	6.5508	86.750	6.8641	0.156
4 h	82.700	6.3173	84.800	5.8318	0.126
6 h	83.750	6.6439	84.900	5.6196	0.406
8 h	81.800	6.1067	85.150	5.7981	0.014
12 h	80.050	5.6657	84.150	6.6931	0.004
24 h	80.850	7.7379	83.450	6.2918	0.103



At 8 hours and 12 hours, Bupivacaine group had a significantly higher heart rate compared to Ropivacaine group, whereas at other time interval there was no significant difference.

Table 4: Comparison of SBP among both the groups at various time interval

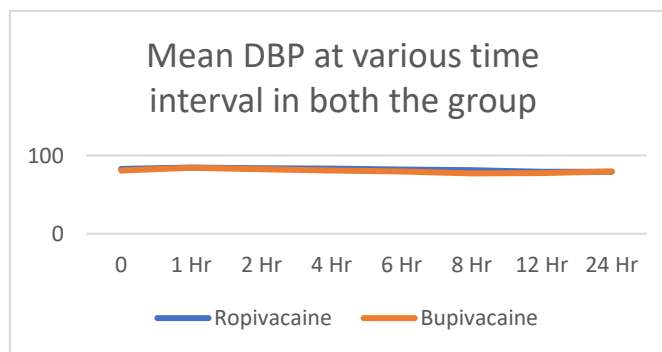
SBP at various time interval	Ropivacaine		Bupivacaine		P value
	Mean	SD	Mean	SD	
0	133.350	9.0626	132.650	10.6832	0.753
1 h	136.150	8.0306	138.000	9.1259	0.339
2 h	136.000	7.5379	136.300	8.4677	0.868
4 h	135.100	5.7815	135.050	8.3388	0.975
6 h	134.400	6.5976	135.050	8.1522	0.696
8 h	133.550	7.2251	132.850	8.1886	0.686
12 h	131.750	6.0117	131.800	8.6386	0.976
24 h	131.650	7.5636	131.900	8.1266	0.887



The difference in SBP was not significant among both the groups at any of the time interval.

Table 5: Comparison of DBP among both the groups at various time interval

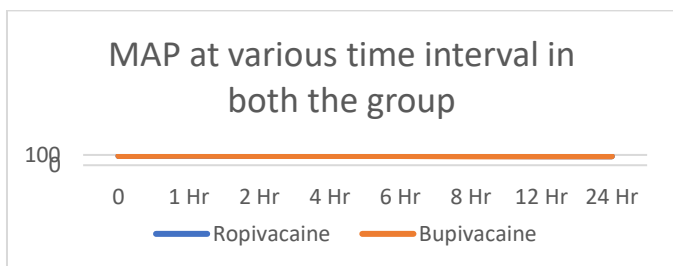
DBP at various time interval	Ropivacaine		Bupivacaine		P value
	Mean	SD	Mean	SD	
0	82.850	5.6729	80.650	8.3805	0.173
1 h	84.550	5.5468	84.250	7.3336	0.837
2 h	83.600	4.3489	82.400	6.2790	0.323
4 h	83.350	5.0917	80.550	7.3588	0.051
6 h	82.000	4.7502	79.350	5.7715	0.028
8 h	81.300	4.8474	77.050	13.0403	0.057
12 h	79.150	4.4581	77.625	7.5233	0.273
24 h	79.250	5.9345	79.700	7.5726	0.768



In Bupivacaine group, a statistically significant lower DBP was seen compared to Ropivacaine group at 6 hours. The difference was not significant at other time interval.

Table 6: Comparison of MAP among both the groups at various time interval

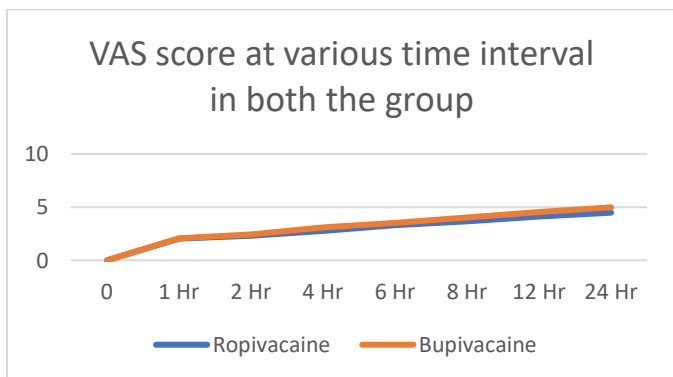
MAP at various time interval	Ropivacaine		Bupivacaine		P value
	Mean	SD	Mean	SD	
0	89.72	5.41	88.19	7.74	0.308
1 h	91.58	5.16	91.95	6.81	0.782
2 h	90.96	3.97	90.33	5.87	0.576
4 h	90.54	3.97	88.85	6.34	0.156
6 h	89.52	4.28	88.13	5.47	0.208
8 h	88.85	4.35	86.09	9.26	0.092
12 h	87.02	3.95	86.12	6.47	0.455
24 h	87.05	5.42	87.39	6.54	0.798



The difference in MAP among both the groups was not statistically significant at any of the time interval.

Table 7: Comparison of VAS score among both the groups at various time interval

VAS score at various time interval	Ropivacaine		Bupivacaine		P value
	Mean	SD	Mean	SD	
0	0.000	0.000	0.000	0.000	1.000
1 h	2.050	0.221	2.075	0.267	0.649
2 h	2.300	0.464	2.425	0.501	0.250
4 h	2.775	0.530	3.100	0.379	0.002
6 h	3.300	0.464	3.525	0.506	0.041
8 h	3.650	0.580	4.025	0.480	0.002
12 h	4.100	0.545	4.525	0.554	0.001
24 h	4.475	0.554	4.975	0.480	<0.001

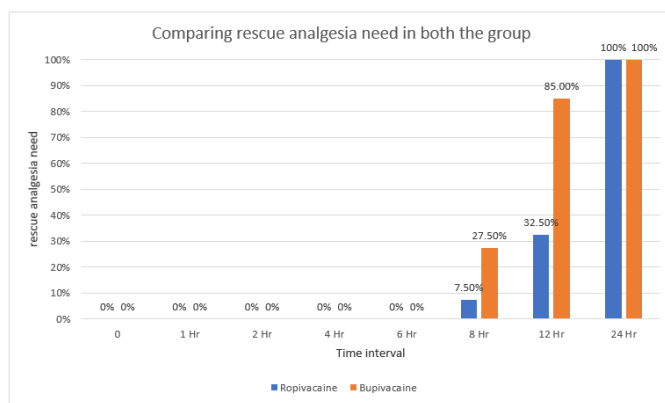


At 4 hours, 6 hours, 8 hours, 12 hours and 24 hours there was a statistically significant lower VAS score in Ropivacaine group compared to Bupivacaine group.

No significant difference in VAS at 0, 1 hour and 2 hours.

Table 8: Comparison of rescue analgesia needed among both the groups at various time interval

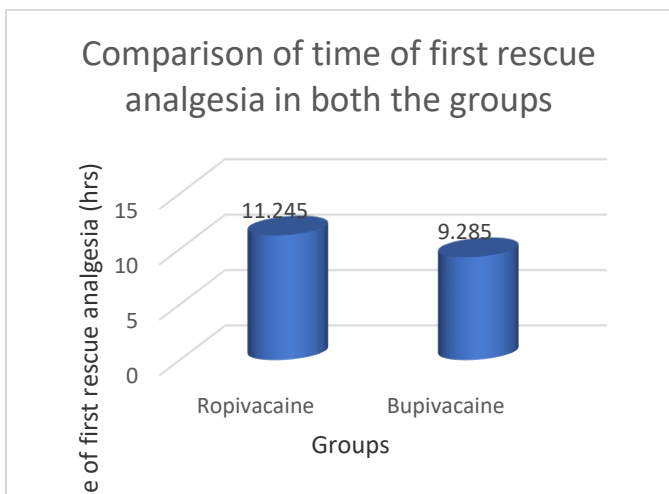
Rescue analgesia need and time interval	Ropivacaine		Bupivacaine		P value
	Frequency	Percentage	Frequency	Percentage	
0	0	0%	0	0%	-
1 h	0	0%	0	0%	-
2 h	0	0%	0	0%	-
4 h	0	0%	0	0%	-
6 h	0	0%	0	0%	-
8 h	3	7.5%	11	27.5%	0.019
12 h	13	32.5%	34	85.0%	<0.001
24 h	40	100%	40	100%	-



The requirement of rescue analgesia was significantly higher in Bupivacaine group compared to Ropivacaine group at 8 hours and 12 hours.

Table 9: Comparison of time of first rescue analgesia in both the groups

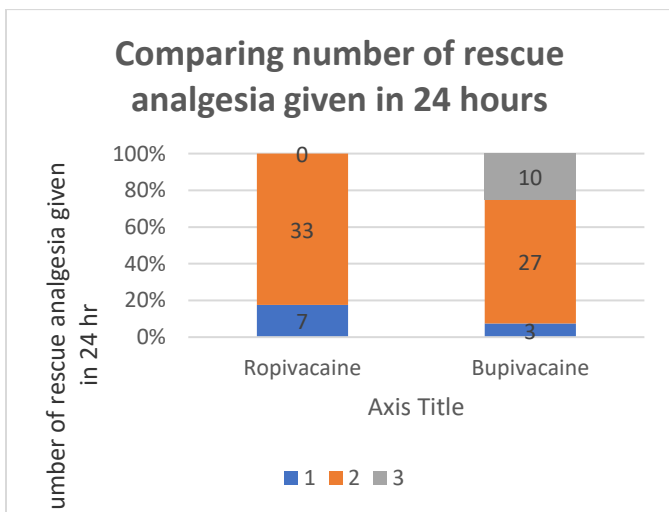
Groups	Time of first rescue analgesia (h)		P value
	Mean	SD	
Ropivacaine	11.245	1.72	<0.001
Bupivacaine	9.285	1.53	Significant



The mean time of the first dose of rescue analgesia was 11.245 hours in Ropivacaine group, whereas it was 9.285 hours in Bupivacaine group.

Table 10: Distribution of study participants based on number of rescue analgesia given in 24 hours.

Number of rescue analgesia given in 24 hours	Ropivacaine		Bupivacaine		P value
	Frequency	Percentage	Frequency	Percentage	
1	7	17.50%	3	7.50%	0.002
2	33	82.50%	27	67.50%	
3	0	0.00%	10	25.00%	
Total	40	100.00%	40	100.00%	



The requirement of number of rescue analgesia was more in Bupivacaine group compared to Ropivacaine group.

Discussion

Laparoscopic cholecystectomy extensively known as a substitute to open cholecystectomy, is a minimally invasive surgery. It is not a pain free procedure even though there is reduced surgical trauma and pain. In the early post-operative period, patients experience moderate to severe pain. Early mobilisation, recovery and discharge are the key objectives of post-operative pain relief.

Laparoscopic cholecystectomy associated pain is multifactorial and multifaceted. The components of it are parietal (abdominal wall), visceral (intra-abdominal) and referral (shoulder tip) and there should be multimodal approach for effective analgesia. Decrease in post-operative stress response, hastening of recovery, early ambulation and inhibition of post-operative morbidity following surgery are done by effective analgesia. Therefore, multimodal analgesia is perhaps the finest means to decrease the post-operative pain.

To evaluate the analgesic effects when local anaesthetics are instilled intraperitoneally into the gall bladder bed many clinical trials have been carried out. Different local anaesthetics like Lignocaine, Bupivacaine, Ropivacaine, Levobupivacaine of varying concentrations were used.

Precise pain assessment scales are used to measure pain. A reliable measurement of pain severity would help regulate therapeutic interventions and estimate the efficacy of treatments.

Following intraperitoneal instillation, we compared the duration of post-operative analgesia and haemodynamic changes after the instillation of Bupivacaine (0.5%) and Ropivacaine (0.5%) in our study.

Group B (n=40) received 25ml of Bupivacaine (0.5%) and group R (n=40) received 25ml of Ropivacaine

(0.5%) instilled intraperitoneally at three sites: 10ml in the subdiaphragmatic region, 10ml in gall bladder bed and 5ml in the omentum, after removal of the gall bladder and before removal of the last trocar. For assessment of post-operative pain, VAS score was noted post-operatively at various time intervals.

In our study entitled, “**A comparative study of intraperitoneal instillation of Bupivacaine (0.5%) and Ropivacaine (0.5%) for post-operative analgesia in laparoscopic cholecystectomy**” majority of patients were in the age group of 40-45 years in both the groups which were comparable and the difference in the age and gender distribution was not statistically significant between them.

There was no statistically significant difference among the groups with regard to age and gender in a study conducted by Rajesh Kumar Meena et al⁹ in 2016, comparing Ropivacaine and Bupivacaine for post-operative analgesia in laparoscopic cholecystectomy.

In our study entitled, “**A comparative study of intraperitoneal instillation of Bupivacaine (0.5%) and Ropivacaine (0.5%) for post-operative analgesia in laparoscopic cholecystectomy**”, Bupivacaine group had significantly higher heart rate compared to Ropivacaine group at 8 hours and 12 hours, and the difference was not significant at other time interval in both the groups.

A study entitled intraperitoneal instillation of Bupivacaine and Ropivacaine for post-operative analgesia in laparoscopic cholecystectomy, by RadheSharan et al⁴ in 2018 concluded that mean heart rate readings in Ropivacaine group were lower compared to Bupivacaine group and was significant at 2, 4, 6 and 8 hours.

In our study entitled, “**A comparative study of intraperitoneal instillation of Bupivacaine (0.5%) and**

Ropivacaine (0.5%) for post-operative analgesia in laparoscopic cholecystectomy”, the difference in SBP was not significant among both the groups at any of the time interval which correlates with the below mentioned study.

Comparison of Intraperitoneal nebulisation of Ropivacaine 0.75% and Bupivacaine 0.5% for post-operative analgesia was done in a study by Porika TS et al¹⁰ in 2018 in laparoscopic surgeries where they concluded that the differences in SBP and MAP were not statistically significant between both the groups.

In our study entitled, “**A comparative study of intraperitoneal instillation of Bupivacaine (0.5%) and Ropivacaine (0.5%) for post-operative analgesia in laparoscopic cholecystectomy**”, a lower DBP was statistically significant in Bupivacaine group compared to Ropivacaine group at 6 hour, but there was no significant difference at other time interval in both the groups. The results of DBP in our study differed from the below-mentioned study.

DBP was lower in Ropivacaine group compared to Bupivacaine group in a study entitled intraperitoneal instillation of Bupivacaine and Ropivacaine for post-operative analgesia in laparoscopic cholecystectomy, by Radhe Sharan et al⁴ in 2018

In our study entitled, “**A comparative study of intraperitoneal instillation of Bupivacaine (0.5%) and Ropivacaine (0.5%) for post-operative analgesia in laparoscopic cholecystectomy**”, Ropivacaine group had a statistically significant lower VAS score compared to Bupivacaine group at 4h, 6h, 8h, 12h and 24 hours. No significant difference in VAS at 0, 1h and 2h were seen. In Bupivacaine group, higher proportion of people needed rescue analgesia compared to Ropivacaine group

at 8h and 12hours. The results were in concordance with the study mentioned below.

The mean VAS score readings were lower in Ropivacaine group compared to Bupivacaine group in the study by RadheSharan et al⁴, entitled intraperitoneal instillation of Bupivacaine and Ropivacaine for post-operative analgesia in laparoscopic cholecystectomy, and were statistically significant at 4, 6 and 8 hours.

In our study entitled, “**A comparative study of intraperitoneal instillation of Bupivacaine (0.5%) and Ropivacaine (0.5%) for post-operative analgesia in laparoscopic cholecystectomy**”, Bupivacaine group had a shorter time to first rescue analgesia compared to Ropivacaine group. The mean duration of first dose of rescue analgesia was lower in Bupivacaine group ($9.285h \pm 1.53$) compared to Ropivacaine group ($11.245h \pm 1.72$), which were correlating with the below-mentioned studies.

Intraperitoneal instillation of local anaesthetics decreases pain intensity scores in early post-operative period, according to the study comparing the effects of intraperitoneal instillation of Bupivacaine and Ropivacaine versus placebo on post-operative pain after laparoscopic cholecystectomy, by Neha T Das et al³, in 2017 and the mean duration of analgesia with Ropivacaine is almost the double of analgesia with Bupivacaine group.

The time to first analgesic requirement was compared in both the groups and was found to be lower in Bupivacaine group in the study entitled intraperitoneal instillation of Bupivacaine and Ropivacaine for post-operative analgesia in laparoscopic cholecystectomy by RadheSharan et al⁴, in 2018. A longer duration of analgesia was found with Ropivacaine group when

compared to Bupivacaine group in a study by Trikoupis et al.

Conclusion

It was concluded from our study entitled “A Comparative Study Of Intraperitoneal Instillation Of Bupivacaine (0.5%) And Ropivacaine (0.5%) For Post-Operative Analgesia In Laparoscopic Cholecystectomy”, that satisfactory post-operative analgesia was provided by both the groups but Ropivacaine(0.5%) seemed to be a better choice compared to Bupivacaine (0.5%) as it provided good quality of post-operative analgesia under steady haemodynamic conditions and also found superior in these two aspects-

1. Prolonged duration of post-operative analgesia.
2. Decreased number of rescue analgesia used in 24 hours.

We conclude that for patients undergoing laparoscopic cholecystectomy, intraperitoneal instillation of local anaesthetic drug is useful for post-operative pain relief and when compared to Bupivacaine (0.5%), intraperitoneal instillation of Ropivacaine (0.5%) is a better analgesic with well-maintained haemodynamic post-operatively.

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