A Comparative Study Of Postoperative Analgesic Efficacy Of Intraperitoneal Nebulization Of Bupivacaine And Fentanyl V/S Ropivacaine And Fentanyl For Laparoscopic Cholecystectomy Surgeries

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Abstract

Due to their minimally invasive nature, laparoscopic operations have a low risk of surgical trauma. The use of Bupivacaine and Ropivacaine, long-acting local anaesthetics that can be administered intra peritoneally to offer effective pain management during the first 24 hours following surgery when combined with an opiate like Fentanyl (causes a delay in discharge). In a randomized prospective clinical trial, a total of 48 patients were randomly allocated to receive either intraperitoneal nebulization with 3ml of (0.5%) Bupivacaine with 100 mcg Fentanyl (Group1) and 3ml of (0.5%) Ropivacaine with 100 mcg Fentanyl (Group-2).Postoperatively SBP, DBP, SpO_2 and HR differences were tested b/w the two groups. VAS scores, age, gender distribution and ASA grade found to be insignificant ($p>0.01$). The dynamic VAS scores were lower in G_1 as compared with G_2, and the analgesic duration was noticeably longer in the Ropivacaine with Fentanyl group. Inferring that using Fentanyl as an adjuvant to an intraperitoneally injected long-acting local anaesthetic like Bupivacaine or Ropivacaine is safe, effective and helps patients be discharged sooner.

Keywords: Ropivacaine, Bupivacaine, Laparoscopic, VAS score

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INTRODUCTION

Surgical pain arises as a result of inflammation from tissue due to trauma. Cholecystectomy is the most common surgery of the biliary tract and the second most common operative procedure performed today. Laparoscopic Cholecystectomy has replaced Open Cholecystectomy as the first choice of treatment for gallstones and inflammation of the gall bladder unless there are any contra indications to the laparoscopic approaches.[1] Although it is believed that laparoscopy has ushered in a pain-free era, the fact remains that patients complain of more visceral pain after laparoscopic Cholecystectomy in contrast to parietal pain experienced in open cholecystectomy. Visceral pain has maximum intensity during the first hour and is exacerbated by coughing, respiratory movements and mobilization and it is a distinctly separate form of pain as compared to somatic pain. [2] Signaling occurs through the enteric nervous system, with a vast net work of distinct and functionally diverse, neuronal sub types. Viscera such as the gall bladder and the covering peritoneum convey unpleasant sensations and autonomic reactions to the injury through different in the vagus nerve. These so-called"silent nociceptors" are activated by intra peritonial inflammation and

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injury.

Different multimodal approaches have been established to ameliorate postoperative pain. These include parenteral analgesics such as non-steroidal anti-inflammatory drugs (NSAIDS), epidural/intra the calopioids, local infiltration with local anesthetics, intrapleural and inter costal nerve blocks as well as intraperitoneal routes that in turn have been explored with local anesthetics and opioids .It is also possible to in still local anesthetics into the peritoneal cavity, thereby blocking visceral afferent signaling and potentially modifying visceral nociception and downstream illness responses.[3] Studies evaluating different techniques of local anesthetic delivery including periportal infiltration, diaphragmatic irrigation, instillation into sub diaphragmatic area, or diffuse instillation have shown conflicting results. Overwhelmingly, too many factors might contribute to the failure of the instillation technique which may be related to the inadequate distribution of local anesthetic throughout the peritoneal surface. In this regard nebulization should provide a uniform spread of LA throughout the peritoneal cavity and thus may be beneficial to improve pain relief after laparoscopic procedures.[4].Many studies have reported that Ropivacaine nebulization significantly reduced pain after Laparoscopic Cholecystectomy in comparison with instillation within the gall bladder bed. The present research objective is to compare the analgesic efficacy of nebulized 0.5% Bupivacaine with 100 mcg Fentanyl and 0.5% Ropivacaine with 100 mcg Fentanyl in patients undergoing elective Laparoscopic Cholecystectomy on the basis of Post-operative pain scores and also to correlate the total consumption of the first rescue analgesic and its complications.

Methods

A prospective randomized double blinded study was carried out in the Department of Anesthesiology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore from 2020-2021. Institutional clearance was obtained, also written informed consent received from all the patients. Sample size was determined based on power analysis by using SAS statistical software considering alpha at 0.05 and beta was 0.85 with marginal error 10% . A total of 24 cases were determined in each group, the patients were classified as per American Society of Anesthesiology (ASA), physical status I and II aged between 18-65years undergoing elective laparoscopic cholecystectomy surgeries were included in this study. Using sealed envelope method, 48 patients were randomly allocated in to two groups. Group 1 has received 3mL of 0.5% Bupivacaine with 100 mcg (2mL) of Fentanyl intraperitoneally at the end of laparoscopic cholecystectomy surgery and Group 2 was received 3mL of (0.5%) Ropivacaine with 100mcg (2mL) of Fentanyl intraperitoneally at the end of laparoscopic cholecystectomy surgery. The following inclusion Criteria was considered viz (i) American Society of Anesthesiologist (ASA)I,II (ii) Elective laparoscopic cholecystectomy surgeries and patients (18-65) years of age. Exclusion criteria was acute pancreatitis, acute post-operative pain other than biliary colic, anti-epileptic therapy, history of alcohol or drug addiction, severe renal or hepatic impairment, allergy to the drugs and amide local anaesthetics, pregnancy and lactation, ischemic heart disease and increased duration, prolonged surgery(>60mins).Each patient had a thoroughly assessed pre anesthetic evaluation and lastly any significant prior and past medical/surgical history was noted. General physical examination, systemic examination and local examination was done. Vital parameters like height, weight, heart rate, NIBP&O_2 saturation were noted and documented. Routine investigations like CBC, Urine Routine, RBS & Serum Electrolytes and other investigations - RFT, LFT, Chest X-Ray, ECG and Covid RT PCR (during COVID pandemic) were done. Patients were kept nil peroral for a minimum of 6 hours. Tab. Alprazolam 0.25mg and Tab. Pantoprazole 40mg tablets were given orally on the night before the surgery to all the patients. VAS score for post-operative pain assessment was explained to the patient and study was conducted asper the standard operating protocol (SOP). All Patients were posted for elective laparoscopic cholecystectomy surgery satisfying the inclusion criteria were preoperatively evaluated, relevantly investiga-

ted and adequately premeditated then shifted to the OT on the day of surgery. NPO status was confirmed and machine was checked as per the checklist. ASA Standard monitors were attached to note the baseline vitals. Premedication with Injection Ondansetron 4mg IV and Midazolam 0.03mg/kg IV & Glycopyrollate 0.2mg IV 30mins before the procedure. A random draw was taken by the Nurse in charge of the OT, the specific group of drugs were loaded and given to the observer, the procedure was performed by the observer. Patients were given general anaesthesia under standard protocols, were pre- oxygenated with 100% Oxygen for 3minutes and then induced with IV Propofol 2mg/ kg body weight and IV Fentanyl 2mcg/kg body weight. Muscle relaxation was achieved with neuromuscular blocker IV Vecuronium 0.1mg/kg. Inhalational agents were started. Under direct laryngescopy, appropriate size endotracheal tube was inserted, cuff was inflated and ETT was fixed after confirming B/L equal air entry by 5 point auscultation. Patients were ventilated intraoperative with (FiO_2 - 40%) O_2 in air and an inhalational agent at respective MAC and neuromuscular blocker Inj. Vecuronium 0.01 mg/kg body weight. Intraoperative Non-invasive Blood Pressure, Heart Rate, SPO_2, $ETCO_2$ and ECG were monitored. At the end of the procedure for the purpose of nebulization; we used an ultrasonic nebulizer. It consists of a container for the drug which was sterilized after every use (ETO) and a silicon tubing which was sterilized as well. This silicone tubing was connected to the umbilical port. The rate of delivery of the drug was 0.5 mL/minute and the size of the aerosols was 5 microns. This allowed an efficient delivery of the local anaesthetic and a uniform spread of the drug throughout the peritoneal cavity. After the completion of the procedure and before the withdrawal of the umbilical port just before the deflation of the pneumoperitoneum; the patient received nebulization with a local anaesthetic. Nebulization was terminated once the nebulizer chamber was found empty. Intra-abdominal pressure was maintained between 12-15 mmHg. Drug was allowed to settle for 5mins before deflation of pneumoperitoneum. The end-tidal carbon dioxide was maintained between (30-35) mm Hg intra operatively by adjusting minute ventilation appropriately. SpO_2 was maintained between (97 -100 %) intra-operatively. Port site infiltration was given with 10ml of 0.5% Bupivacaine at the end of the surgery in both the groups. Once the procedure was completed inhalational agent and air were cut off. Thorough oropharyngeal suctioning was done. After noticing spontaneous breathing efforts reversal of 0.01mg/kg Glycopyrollate + 0.05mg/kg Neostigmine was given. Patient was extubated when adequate muscle power was elicited; and then shifted to PACU for further monitoring. Post-operative course: Postoperatively the patients were given oxygen support with Hudson's mask (5L/min) for 1 hour. Postoperatively patients were monitored for hemodynamic changes including: Heart rate& SBP. All the above mentioned findings were recorded on shifting to recovery room, every 15mins for the1st hour followed by 2, 4, 6, 12 and 24 hours intervals. Time taken for first rescue analgesic, total analgesic consumed, time to firstun assisted ambulation and duration of hospital stay were also noted.

Results

Therewerenoclinicalorstatisticallysignificantdifferencesinthedemographicandhemodynamicprofiles of patients and the two groups were comparable.

Table 1: Mean age and weight of the patients in Group 1and 2

Attributes	G_1 (n=24)	G_2 (n=24)	P-Value
	Mean ± SD	Mean ± SD	
Age (in years)	47.17±10.87	41.79±13.70	P>0.01
Weight (kgs)	56.58±3.12	55.75±7.58	P>0.01
ASA			
ASA I	19(79.2%)	17(70.8%)	
ASAII	5(20.8%)	7(29.2%)	P>0.01

A total of48patients were included in this present study. The male to female ratio was 26: 22 with mean age was 47.17±10.87 years and 41.79±13.70years in group 1 & 2 respectively .There was no statistically significant difference (P-Value >0.62) (Table 1) between the two groups. An overall mean weight of group 1 was 56.58±3.12 kgs and 55.75±7.58 kgs in group-2 respectively (p=0.13). Both the groups were comparable in terms of the ASA

status of either ASA I or II with (70-79%) of the sample falling within the ASA I group. A group -1 had 19 / 5 of ASA I /II respectively and Group-2 had 17 / 7 of ASA I/II respectively, there was no statistical significant difference (P Value >0.05) between ASA and body weight.

Table 2: Trends in systolic blood pressure

Time period	G_1(n=24)	G_2(n=24)	P-value
	Mean ± SD	Mean ± SD	
@Baseline	122.56 ± 14.53	126.24 ± 12.17	P>0.01
@0 min	128.0 ± 14.23	126.24 ± 11.60	P>0.01
@15 min	127.7 ± 14.20	126.20 ± 11.61	P>0.01
@30 min	127.2 ± 14.24	126.12 ± 11.58	P>0.01
@45 min	126.9 ± 14.26	125.92 ± 11.60	P>0.01
@1 hour	126.80± 14.32	125.88 ±11.63	P>0.01
@2 hours	126.32 ± 14.03	124.76 ± 11.67	P>0.01
@4 hours	124.0 ± 13.57	123.20 ± 12.06	P>0.01
@6 hours	120.56 ± 13.46	117.52 ± 11.33	P>0.01
@12 hours	113.92 ± 13.41	115.76 ± 11.92	P>0.01
@24 hours	110.96 ± 13.83	115.76 ± 10.08	P>0.01

Table 3: Mean DBP at different time intervals

Time period	G_1(n=24)	G_2(n=24)	P- value
	Mean ± SD	Mean ± SD	
@Baseline	82.16 ± 7.70	80.96 ± 7.23	P>0.01
@0 min	80.20 ± 7.40	81.0 ± 7.19	P>0.01
@15 min	80.18 ± 7.40	81.0 ± 7.12	P>0.01
@30 min	80.00 ± 7.36	80.0 ± 7.18	P>0.01
@45 min	80.20 ± 7.40	81.0 ± 7.19	P>0.01
@1 hour	79.80 ± 6.85	80.52 ± 7.30	P>0.01
@2 hours	79.81 ± 7.30	80.33 ± 7.54	P>0.01
@4 hours	79.40 ± 6.25	78.92 ± 6.68	P>0.01
@6 hours	77.20 ± 7.02	77.92 ± 7.10	P>0.01
@12 hours	74.88 ± 7.37	77.12 ± 7.12	P>0.01
@24 hours	74.16 ± 7.32	76.36 ± 6.94	P>0.01

Table 4: Mean HR changes

Time period	G_1(n=24)	G_2(n=24)	P - value
	Mean ± SD	Mean ± SD	
@Baseline	96.0 ± 9.60	95.2 ± 9.00	P>0.01
@0 min	88.36 ± 9.10	87.28 ± 8.70	P>0.01
@15 min	86.48 ± 8.43	86.04 ± 7.41	P>0.01
@30 min	85.83 ± 8.20	84.04 ± 7.21	P>0.01
@45 min	82.48 ± 7.83	83.04 ± 7.18	P>0.01
@1 hour	78.49 ± 7.43	82.04 ± 7.41	P>0.01
@2 hours	77.60 ± 7.38	81.09 ± 7.04	P>0.01
@4 hours	76.32 ± 7.81	80.71 ±.7.83	P>0.01
@6 hours	75.00 ± 8.08	79.12 ± 7.42	P>0.01
@12 hours	74.36 ± 8.09	78.92 ± 8.06	P>0.01
@24 hours	74.16 ± 8.40	78.52 ± 8.34	P>0.01

Table 5: Changes in mean SpO_2

Time period	G_1(n=24)	G_2(n=24)	P – value
	Mean ± SD	Mean ± SD	
@Baseline	98.64 ± 0.70	98.88 ± 0.72	P>0.01
@0 min	98.81 ± 0.70	99.00 ± 0.70	P>0.01
@15 min	98.81 ± 0.70	99.21 ± 0.72	P>0.01
@30 min	98.80 ± 0.70	99.00 ± 0.70	P>0.01
@45 min	98.67 ± 0.68	99.00 ± 0.69	P>0.01
@1 hour	98.45 ± 0.65	98.60 ± 0.64	P>0.01
@2 hours	98.68 ± 0.80	98.84 ± 0.74	P>0.01
@4 hours	98.37 ± 0.81	98.56 ± 0.76	P>0.01
@6 hours	98.25 ± 0.66	98.47 ± 0.71	P>0.01
@12 hours	98.32 ± 0.80	98.60 ± 0.86	P>0.01
@24 hours	98.36 ± 0.75	98.75 ± 0.73	P>0.01

Static VAS Scores: Mean Static VAS scores were not statistically significant at any of the measured points of time frame

Table 6: Mean Static VAS scores

Time period	G_1(n=24)	G_2(n=24)	P - value
	Mean ± SD	Mean ± SD	
@0 min	14.01 ± 1.7	14.02 ± 1.82	P>0.01
@15 min	14.00 ± 1.62	13.65 ± 1.42	P>0.01
@30 min	13.9 ± 1.38	13.20 ± 1.28	P>0.01
@45 min	13.8 ±1.56	13 ±1.26	P>0.01
@1 hour	13.4 ± 1.22	12.80 ± 1.22	P>0.01
@2 hours	12.96 ± 1.64	12.60 ± 1.48	P>0.01
@4 hours	13.11± 1.65	12.45± 1.38	P>0.01
@6 hours	13.14 ± 1.58	12.4 ± 1.29	P>0.01
@12hours	12.36 ± 1.62	12.1 ± 1.20	P>0.01
@24hours	9.38± 1.60	9.43± 1.46	P>0.01

Table 7: Mean Dynamic VAS Scores

Time period	G_1 (n=24) Mean ± SD	G_2 (n=24) Mean ± SD	P - value
@0 min	24.62 ± 1.7	23.05 ± 1.82	≤0.003
@15 min	24.57± 1.62	22.95 ± 1.42	≤0.0006
@30 min	23.9 ± 1.38	22.77 ± 1.26	≤0.005
@45 min	23.8 ±1.56	22.45 ±1.24	≤0.0018
@1 hour	23.70 ± 1.22	22.32 ± 1.20	≤0.000
@2 hours	22.76 ± 1.64	21.21 ± 1.48	≤0.0013
@4 hours	23.13± 1.65	21.32± 1.38	≤0.0002
@6 hours	23.24 ± 1.58	21.78 ± 1.29	≤0.000
@12hours	22.36 ± 1.62	20.08 ± 1.20	≤0.0001
@24hours	16.37± 1.60	15.03± 1.46	≤0.004

Mean dynamic VAS Scores were found to be significantly lesser in Group-2 than Group-1 throughout the first 24 hours postoperatively with a P-value **<** 0.05**.** Time taken for first rescue analgesic and total analgesic consumption: Mean Time taken for administration of rescue analgesia was 8.49+0.6 hours in Ropivacaine group and 7.52+0.5hours in Bupivacaine group which was statistically significant (p = 0.0001**).**

Earliest and longest time of administering rescue analgesia in group-2 was 7 and 9.1 hours respectively and ingroup1 was 6.6 and 8.5hours respectively. Mean of Total rescue analgesic dose required in group 2was 95+36.2 mgvs.114.7+37.5mg in group1 which was not very statistically significant (p = 0.06).

Table8: Mean time for first rescue analgesic and total analgesic consumption

Variable	G_1 (n=24) Mean ±SD	G_2 (n=24) Mean ± SD	P-Value
Time for rescue analgesia (in hours)	7.52 ± 0.5	8.49 ± 0.6	≤0.0001
Total dose (in mg)	114.7 ± 37.5	95 ± 36.2	>0.07

Time to first unassisted ambulation: Mean time required for unassisted ambulation was 13.21 +/-0.7 hrs vs.12.96+/- 0.6 hrs in groups 1 and 2 respectively and the difference was not statistically very significant (p=0.3).The mean time for rescue analgesia and total analgesia consumption was estimated by ROC, group1 & 2 significantly differ (P<0.01) with each Coefficient of determination R^2(0.85%).

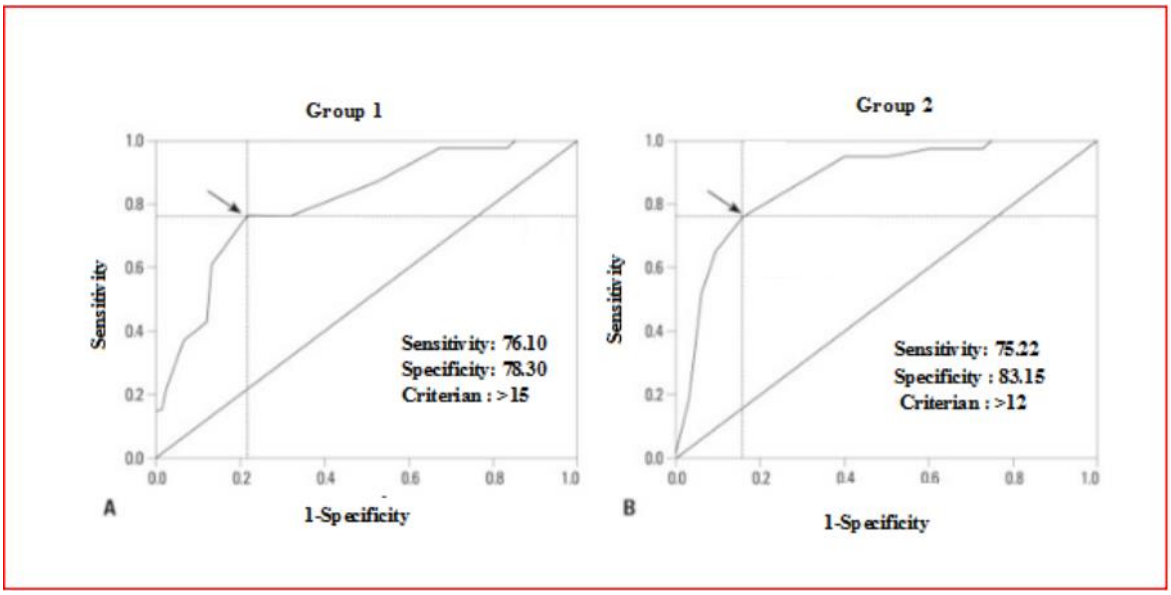

Fig1. ROC curve in Group 1&2

Table 9 Time taken for first unassisted ambulation

Early ambulation (inhours)	G_1(n=24)	G_2(n=24)	P-Value
Mean ± SD	13.21 ± 0.7	12.96 ± 0.6	0.32 (not significant)

However, a total of 15 individuals in group B (50% of the study group) and 8individuals in group R (26.6% of the study group) required 2nd dose of rescue analgesia in 24 hours. This probably reflects the difference of efficacy in analgesia provided by Ropivacaine and Bupivacaine. The mean duration of hospital stay was 42.52=/- 1.57 hours and 43.02+/- 1.42 hours in group2and group 1 respectively which was statistically insignificant None of the patients in either of the study groups complained of shoulder tip pain proving (100%) relief with intraperitoneal nebulization of Bupivacaine/Ropivacaine with Fentanyl. No patients belonging to either group complained of post-operative nausea and vomiting, pruritis, hypotension, bradycardia, urinary retension or respiratory depression. Therefore, the study drugs are efficacious and the route of administration is safe for providing post operative analgesia after laparoscopic cholecystectomy.

Discussion

This study compares the postoperative analgesic efficacy of intraperitoneally nebulized Bupivacaine and Ropivacaine. Inj. Fentanyl has been used as an additive in both groups, along with local anesthetic agents for intraperitoneal nebulization. Laparoscopic cholecystectomy is a minimally invasive surgery. The essence of a daycare surgery is early discharge, through better post-operative pain relief which helps in early ambulation and recovery. Laparoscopic surgeries have a better surgical outcome in terms of lesser post-operative pain and relatively minor surgical trauma. Some have evolved as daycare surgeries owing to: Significantly reduced stress responses, Lesser Postoperative pain, improved postoperative

pulmonary function, reduced overall morbidity. Thus resulting in rapid recovery and early ambulation, reduced risk of DVT and speeding up the return to normal activities. Excessive pain, nausea, vomiting, fatigue and inability to ambulate without assistance may delay the fast-tracking of patients making it difficult to perform minimally invasive procedures under daycare. Hence, an optimal postoperative pain control technique that is simple, safe, effective, producing minimal side effects that facilitates rapid recovery is the need of the hour. Studies have shown that there has been an underestimation of pain leading to under treatment especially in minimally invasive surgeries. About (30 – 40 %) of the patients discharged on a daycare basis suffer from moderate-severe pain in the first 24-48 hrs, being significant enough to interfere with sleep and daily functioning. Literature reveals studies done in the past to differentiate and understand the various anatomical areas involved in the generation and modulation of pain after laparoscopic cholecystectomy. Pain after LC has a multifactorial origin: Visceral, Parietal and Shoulder tip pain. Visceral pain is due to the damaged free nerve endings of the peritoneum caused by stretching during pneumoperitoneum and inflamed cholecystectomy wounds. The vagus nerve innervates the visceral peritoneum via silent nociceptors. These free nerve endings are activated by inflammation leading to poorly localized visceral pain. Parietal pain happens to be of less intensity owing to the small incisions causing limited damage to the abdominal wall. This can be overcome by port site infiltration of LA. Shoulder tip pain is mainly due to the irritation of the phrenic nerve. Joris et al., 1995 highlighted the characteristics of pain after LC and concluded that visceral pain is predominant during the first 24hours post-operatively, is short-lived and increases on coughing though unaffected by mobilization. [5]Studies evaluating intraperitoneal local anesthetic instillation for pain relief after laparoscopic cholecystectomy have provided conflicting results. One of the factors that might contribute to the failure of the instillation technique may be related to the inadequate distribution of local anesthetic throughout the peritoneal surface. In contrast, nebulization provides a uniform spread of local anesthetics throughout the peritoneal cavity and thus may be beneficial to improve pain relief after laparoscopic procedures. Kahokehr et al., 2010 reviewed 30 randomized controlled trials in laparoscopic cholecystectomy. He found that IPLA reduces pain, opioid use, and the stress response. He thus concluded that further trials are unnecessary in this regard.[6] A systematic review of laparoscopic gastric procedures included three studies on obesity surgery and two on fundoplication. In this study IPLA was found to have reduced pain scores and lesser shoulder tip pain.

Intraperitoneal Route

The intra-peritoneal route has been chosen because it provides analgesia by visceral afferent signaling blockade by the LA thereby potentially modifying visceral nociception. The local anesthetic inhibits nociception by affecting nerve membrane- associated proteins and by inhibiting the release and action of prostaglandins and other agents that sensitize or stimulate the nociceptors and contribute to inflammation. It has been proven that in pressurized intraperitoneal aerosol chemotherapy (PIPAC) the macroscopic stain distribution throughout the entire peritoneal cavity was homogeneous in the abdominal cavity including the small bowel and anterior abdominal wall and hidden surfaces such as the inferior aspect of the liver and the hilum of the liver. Thus validating the fact that nebulizing local anaesthetic intraperitoneally provides good coverage of almost the entire abdominal cavity. Alkhamesi et al.,2007 utilized a novel aerosolization system that has been proven to be successful in delivering intra-peritoneal local anesthetics to treat postoperative pain.[7]

Bupivacaine

(Kang H et al., 2014) concluded that the use of IPLA results in a statistically significant reduction in pain after LC, and administration of intraperitoneal Bupivacaine is most effective in abdominal pain relief.[8](Toleska et al.,2018) also supported the intraperitoneal instillation of Bupivacaine, as it provides good analgesia in the postoperative period after laparoscopic

cholecystectomy.[9] (Frelich, et al., 2008). In their study of intra-peritoneal aerosolization of Bupivacaine undergoing Robotic-assisted laparoscopic pyeloplasty have concluded that it is a simple, effective and low-cost method to reduce postoperative pain in children undergoing laparoscopic pyeloplasty.[10] Zanetta, et al., 2012in their study using intraperitoneal nebulization of Bupivacaine in children undergoing robotic-assisted laparoscopic reconstructive surgery concluded that plasma levels of Bupivacaine were lower probably due to reduced systemic absorption thus improved safety.[11] (Alkhamesi et al.,2007). in their study on patients undergoing laparoscopic Roux En Y gastric bypass using Bupivacaine aerosolization technique to reduce postoperative pain have found that mean pain scores over 24 hours were not statistically significant (p=0.52). This may be due to their use of PCA regularly even if they had no significant pain.[7]

Ropivacaine

Labaille et al., 2002 demonstrated in his study that fractionated injection of 100 mg of intraperitoneal Ropivacaine produces post operative analgesia after laparoscopic cholecystectomy better than what was obtained with an intraperitoneal placebo. Increasing the dose to 300 mg did not improve clinical effectiveness but led to excessively large plasma concentrations.[12]Kaufman, et al.,2008. in their randomized study for pain relief by continuous intra- peritoneal nebulization of Ropivacaine during gynecological laparoscopic surgeries observed that no significant difference existed between the groups in postoperative Visual Analog Scale scores including visceral, abdominal wall, and shoulder pain during rest and during cough at the different time frames. This might be due to the use of Fentanyl for every 20% rise in MAP intra-operatively and Diclofenac per rectal after induction which might have masked early pain. Also, a sample size of 40 may not have been adequate to effectively evaluate the results.[13] Ingelmo, et al.,2013 in their randomized controlled trail compared Ropivacaine nebulization versus Normal Saline for postoperative analgesia in laparoscopic cholecystectomy and obtained results with a 33% reduction in dynamic VAS scores. Kaufman, et al.2008 in their study evaluating pain relief by continuous intra-peritoneal nebulization of Ropivacaine in gynecological laparoscopic surgeries found that it didn't improve patient's outcomes in terms of intraoperative and postoperative pain along with consumption of analgesics that indicated further research.[13]S. Porika et al compared the efficacy of intraperitoneally nebulized Bupivacaine and Ropivacaine. It was found that Ropivacaine had better efficacy than Bupivacaine along with a longer duration of action. This is the rationale for comparing Ropivacaine and Bupivacaine in our study.[14]

Use of Fentanyl

(Bharti Gupta et al., 2011) opined that intraperitoneal instillation of Bupivacaine in combination with Dexmedetomidine or Fentanyl significantly reduced postoperative pain scores in comparison to Bupivacaine alone, in patients undergoing ambulatory laparoscopic cholecystectomy. They however concluded that, Fentanyl may be preferred over Dexmedetomidine, as it caused lesser sedation and achieved a better PADS score.[13] according to their study the combination of intraperitoneal Bupivacaine and Fentanyl is superior to the plain Bupivacaine for the relief of postoperative pain in patients undergoing laparoscopic surgery without any significant increase in adverse events. They also opined that nebulization results in better and uniform dispersion of analgesic drug when given intraperitoneally. They also concluded that, intraperitoneal Ropivacaine nebulization, with or without Fentanyl was highly effective in providing postoperative analgesia and decreased the incidence of shoulder pain. Furthermore, the addition of Fentanyl to ropivacaine prolongs the duration of analgesia. The results of these studies formed the basis for the present study, where the effects of intraperitoneal nebulization of Ropivacaine 0.5% (3ML/ 15 MG) with Bupivacaine0.5% (3ML /15 mg) for laparoscopic surgeries have been compared using an ultrasonic nebulizer available in our setting. The finding of our study is that in comparison with the patients belonging to the Bupivacaine + Fentanyl group, the patients of the Ropivacaine + Fentanyl group experienced statistically significant

reduced dynamic VAS scores in the first 24 hours (P < 0.05). Static VAS scores were however not statistically significant over 24 hours.

Time for the first requirement of rescue analgesic

In our study the time for the first requirement of rescue analgesia is also less in Group-1 when compared to the Group-2 of patients [7.56 ± 0.5(group-1); 8.43 ± 0.6(group-2)] and it was found to be statistically significant (P=0.0001).(Solankhi Rekha, et al., 2014) in their study comparing intraperitoneal instillation versus nebulization for laparoscopic surgeries for postoperative pain relief using Ropivacaine plus morphine in either group found that the requirement for first rescue analgesia was 17.57+/- 0.02 hours. It is almost twice that compared to the present study which might have been due to the addition of fentanyl. In their study observed that the pharmacokinetic profile of Ropivacaine nebulization is similar to direct intraperitoneal instillation but with a lower absorption rate, resulting in prolonged duration of analgesia. There was a reduction in the total analgesic consumed over 24 hours though not quite statistically Significant (P=0.06).[15](Ingelmo, et al.,2013)found that the morphine requirements were reduced by 41% in the Ropivacaine nebulization group.[14]

Time of unassisted ambulation

Time of unassisted ambulation were similar [13.20 ± 0.7 (Group-1)] [12.96 ± 0.6(Group-2)] [P-value = 0.32 (not significant)].(Catenacci, et al., 2015) concluded that Ropivacaine nebulization resulted in early mobility postoperatively and time taken for unassisted ambulation was 12+/-6 hours.[18](Ingelmo, et al.,2013)observed that Ropivacaine nebulization was associated with early mobility (10- 12 hours vs. 18 hours i.e. 44% reduction in time required for early ambulation in comparison with Saline controls).[14](Marata Somaini, et al., 2014) found that patients after receiving Ropivacaine nebulization could walk without assistance within 12 hours of awakening.[19]

Shoulder tip pain

None of the patients belonging to either group in our study complained of shoulder tip pain.(Ingelmo, et al.,2013) observed that there was no incidence of shoulder tip pain in the Ropivacaine nebulization group as compared to Normal Saline control with a 100% reduction in shoulder tip pain.[14] (Solanki Rekha, et al., 2014) found that the incidence of shoulder tip pain was zero in the Ropivacaine nebulization group. Instillation of local anesthetics in the supine position might prevent its flow over the celiac plexus and Phrenic nerve endings whereas nebulization provides uniform distribution giving better results.[16]

Volume and dose nebulized in the present study

In our study, the volume of the drug nebulized was 5 ml corresponding to 15 mg of Ropivacaine 0.5% and 15 mg of Bupivacaine 0.5% with 100 mcg of Fentanyl (2mL). (Ingelmo, et al.,2013)used 30 mg 1% 3 ml Ropivacaine in their studies conducted on patients undergoing laparoscopic gynecological surgeries and laparoscopic cholecystectomies respectively and obtained statistically significant pain relief after surgery.[14](Labaille, et al., 2002) used intra-peritoneal Ropivacaine during laparoscopic cholecystectomy in the dose of 100 mg and 300 mg and found a reduction in postoperative pain. However, they did not find any statistically significant difference in visceral pain scores, time to first rescue morphine in PACU and incidence of PONV.[12] The smaller dosage provided similar analgesia with significantly smaller plasma concentrations than the larger dosage. Hemodynamic parameters post-operatively had no statistically significant differences in SBP and DBP of both the groups at any given point of time. Postoperatively there was no significant difference between MAP of both the groups at any of the times measured. (Kaufman, et al.,2008). in their study found that no significant differences existed between the groups during surgery and at the recovery room in terms of mean arterial blood pressure (p= 0.42) or heart rate (p=0.60). This difference was not found regarding heart rate. [13](Solankhi Rekha, et al., 2014) in their analysis observed that there was no significant difference in hemodynamic changes in intra-

operative as well as postoperative periods between instillation and nebulization groups. [12]

Signs of toxicity

Signs of toxicity such as arrhythmias, hypotension, urticaria, urinary retention were not noted in any of the two groups in the present study. Hence, we did not find the need to record the clinical signs of local anesthetic systemic toxicity amongst all the previous studies.

Post-operative nausea and vomiting

There were no signs of nausea or vomiting in any of the patients in the present study. In the study conducted by (Solankhi Rekha, et al., 2014) none presented with nausea, and 2 out of 30 in the nebulization group presented with vomiting. It would have been probably due to the more emetogenic potential of Tramadol given postoperatively.[12] A study by (Goldstein, et al., 2000) comparing installation of Bupivacaine with that of Ropivacaine at the sub-diaphragmatic and surgical sites showed that 20 ml of 0.75% Ropivacaine provided significantly better analgesia than 20 ml of 0.5% Bupivacaine in gynecologic laparoscopy. Both local anesthetics were equally effective in the prevention of PONV. [19]

Nebulization system

In our study, the nebulization system is an ultrasonic type nebulizer generating particles with the size of the aerosols being 5 microns at the rate of 0.5 mL /minute. Zimmer and colleagues used the Insuflow device, which is a hot evaporation-based nebulizer. It is not surprising that these authors did not observe any analgesic benefits from nebulizing Bupivacaine 0.5% (10 ml), because hot evaporation enables only evaporation of the solvent (e.g. water) and not of the solute (e.g. local anesthetic), thus making the device inefficient in delivering the local anesthetic into the peritoneal cavity. This suggests that studies evaluating the effects of peritoneal nebulization should use a device suitable to deliver the local anesthetic. One of the limitations of the nebulization technique is that the size of the droplets being small creates a foggy environment, which may interfere with the surgeon's vision. In the present study fogging was not a limiting problem as the nebulization was done at the end of the surgery. A low volume of the drug was used intentionally to reduce the time required for nebulization. Concluded that both Bupivacaine and Ropivacaine are safe and similarly efficacious in reducing postoperative pain following intra-peritoneal nebulization in laparoscopic surgeries, and Ropivacaine nebulization significantly reduced dynamic VAS scores over 24 hours. Prolonged duration of analgesia was noted with Ropivacaine nebulization. Total analgesic required over 24 hours was less with Ropivacaine use. Ropivacaine group could ambulate early. No signs of local anesthetic allergy and toxicity were observed. Furthermore, no studies have been conducted to compare the efficacy of Bupivacaine and Ropivacaine with the addition of an opioid like Fentanyl.

Conclusion

It is concluded that, both the drugs used in our study, Bupivacaine and Ropivacaine with Fentanyl as an adjuvant when nebulized intraperitoneally for post-operative pain relief were found to be efficacious following laparoscopic cholecystectomy. Significant reduction in dynamic VAS scores was noted over 24 hours amongst the patients belonging to Ropivacaine with Fentanyl nebulization group. The duration of analgesia was found to be prolonged with Ropivacaine+ Fentanyl nebulization. With the use of Ropivacaine+ Fentanyl intraperitoneally, the total analgesic required over 24 hours was found to be lesser, when compared with Bupivacaine +Fentanyl. Also, the patients who received Ropivacaine+ Fentanyl combination could ambulate earlier. There was no evidence of hypersensitivity/ allergy or systemic toxicity with the use of local anesthetics intraperitoneally. Use of Fentanyl as an adjuvant to intraperitoneal local anaesthetics reduces not just the intensity of pain but also the need for rescue analgesics, thereby facilitating early ambulation of the patients. There were no additional opioid-related side effects from the use of Fentanyl. Fentanyl as an adjuvant to intraperitoneally nebulized local anesthetics, besides providing better analgesia, also aids in prolonging the

duration of analgesia, thereby facilitating early ambulation and early discharge of patients without causing any side- effects. Thus, making it safe and ideal for daycare laparoscopic surgeries.

Limitation

Intraperitoneal nebulization of local anaesthetics if done at the beginning and at the end of the surgery is very advantageous but the average duration is more than 10mins for 5ml to be nebulized. Also, studies have shown that nebulization done at the beginning of the surgery caused a foggy environment impairing the surgeons' view. To overcome these limitations faced earlier, we have conducted the intraperitoneal nebulization only at the end of the surgery. Another limitation of the study was that the concentration of Ropivacaine and Bupivacaine used were not of equivalent dosage. No studies have been conducted in the past comparing these two drug dosages, therefore chosen for the current study.

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