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COMPARATIVE EVALUATION OF CLINICAL EFFICACY OF INTRAPERITONEAL ROPIVACAINE WITH AND WITHOUT FENTANYL FOR POST-OPERATIVE ANALGESIA AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

Background: The improved understanding of origin of abdominal and shoulder pain after laparoscopic procedures led to the use of intra peritoneal and port site instillation of local anaesthetic to reduce post-operative pain. Combinations of intraperitoneal local anaesthetics with many opioids have been studied in past and it was proved that they provide additional analgesic benefits. **Material and methods:** 106 ASA grade I and II patients of age 20 to 60 years of either sex weighing 40 to 70 kg undergoing laparascopic cholecystectomy under general anaesthesia were enrolled for the present study after written informed consent and institutional ethical committee cleareance. Patients were randomized into two groups , Group I (n=53): Patients received 30ml of 0.5% ropivacaine with 2ml Normal Saline. Group II (n=53): Patients received 30ml of 0.5% ropivacaine with fentanyl 100 mcg (2 ml). General anaesthesia was standardized. VAS, VRS scores, hemodynamics, total amount of rescue analgesic and side effects were noted at regular intervals. **Results:** VAS and VRS score were significantly lower in ropivacaine plus fentanyl group in comparisons to ropivacaine alone group at most of the time intervals. Hemodynamics was comparable between the two groups. Total Rescue analgesic were also significantly ow in ropivacaine plus fentanyl group side effects were comparable between two group. **Conclusion:** Intraperitoneal instillation of ropivacaine with fentanyl reduces not only the intensity of visceral, parietal and shoulder pain but also the total rescue analgesic dose consumption.

KEYWORDS :

INTRODUCTION

Laparoscopic cholecystectomy is the standard technique for gall bladder surgeries these days. These surgeries have less post operative pain and smooth recovery than conventional open cholecystectomies. Visceral pain after laparoscopic surgery results from the stretching of the intraabdominal cavity and peritoneal inflammation, shoulder pain results from phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity and parietal pain is of much less intensity because of smaller incisions.1
The improved understanding of origin of abdominal and shoulder pain after laparoscopic procedures led to the use of intra peritoneal and port site instillation of local anaesthetic to reduce post-operative pain.2 The rationale for choosing the intraperitoneal route is to block the visceral afferent signalling and potentially modifying visceral nociception and provide analgesia. The local anaesthetic 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.3 However, absorption from large peritoneal surface may also occur, which may be a further mechanism of analgesia.

Combinations of intraperitoneal local anaesthetics with many opioids have been studied in past and it was proved that they provide additional analgesic benefits but intraperitoneal morphine was found to be less effective in providing analgesia while meperidine achieved adequate pain relief. Administration of lipophilic opioid (Fentanyl or Meperidine) in the peritoneal cavity provides better analgesia. The presence of inflammation has been found to enhance the efficacy of peripherally applied opioids.4 This is because inflammation disrupts the perineurium as well as increases the number of peripheral sensory nerve terminals.5
Therefore, this single centre prospective randomized double blind clinical study was conducted to compare the effectiveness of intraperitoneal ropivacaine with or without fentanyl for postoperative analgesia after laparoscopic surgery.

Materials and methods

After approval from institutional ethical committee patients scheduled for elective Laparoscopic cholecystectomy under general anaesthesia were enrolled for the present study with written informed consent. Patients were randomized into two groups (n = 53) using a computer generated table of random numbers. Group I (n=53): Patients received 30ml of 0.5% ropivacaine with 2ml Normal Saline. Group II (n=53): Patients received 30ml of 0.5% ropivacaine with fentanyl 100 mcg (2 ml).

Group allocation and study drug preparation in group labelled syringes were done by anaesthesiologist who were unaware of the study and drug was instilled by the surgeon under the observation of another resident who was unaware of the study. Data was collected by resident who was blinded about the group allocation.
All surgeries were carried out on ASA grade I to II, age 20 to 60 years of either sex weighing 40 to 70 kg under general anaesthesia. Patients excluded were those taking non-steroidal anti-inflammatory drugs (NSAIDS) or any other analgesic, history of alcohol or drug abuse, confirmed local anaesthetic sensitivity, chronic pain syndrome, emergency operation, intraperitoneal placement of drain, history of malignancy, history of psychiatric illnesses, Restrictive lung disease, Obesity and known case of obstructive sleep apnea.

On arrival to operation theatre, routine monitoring was commenced and baseline vital parameters of heart rate, non-invasive arterial pressure including systolic, diastolic and mean arterial pressure, peripheral oxygen saturation (SpO2) and electrocardiogram (ECG) were recorded. An intravenous line was

secured and lactate Ringer solution was started.

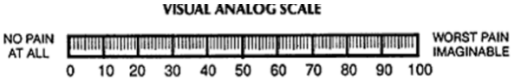
All patients received pre-medication of Inj. Midazolam 0.05 mg/kg, Inj. Glycopyrrolate 0.2 mg and Inj. Ondansetron 4 mg, Inj.fentanyl 2mcg/kg intravenously 10 minutes before induction. After pre oxygenation for 3 min with 100% oxygen by face mask, patient was induced with propofol 2mg/kg, till loss of verbal command, followed by vecuronium bromide 0.1 mg/kg to facilitate direct laryngoscopy and intubation in all patients after ensuring complete relaxation and jaw opening. All patients were intubated with Macintosh curve blade laryngoscope within 15 seconds with proper sized cuffed endotracheal tube. Anesthesia was maintained with isoflurane, nitrous oxide 60% in Oxygen. After intubation injection diclofenac sodium (75mg) was given intramuscularly. The patients were mechanically ventilated to keep normocapnia. Supplemental vecuronium was given to maintain neuromuscular blockade as and when needed.

Patients were placed in 15° to 20° reverse trendelenberg position. During laparoscopy, intraabdominal pressure was maintained at 12-14 mmHg. After completion of surgery and achieving hemostasis, local anaesthetic solution was be injected intra-peritoneally before the removal of trocar at the end of the surgery, in trendelenburg's position 20 degree to facilitate dispersion of drug solution in sub hepatic region. Local anaesthetic solution was given as follows: the surgeon sprayed 10 mL of solution into the hepato-diaphragmatic space, 10 mL in the area of the gallbladder bed and 10 ml was infiltrated around wounds of surgical ports. Patients of Group I will be given 30ml of 0.5% Ropivacaine with 2ml NS and Group II will be given 30ml of 0.5% Ropivacaine with fentanyl (100mcg) 2ml intraperitoneally.

At the end of surgery residual neuromuscular blockade was antagonized with appropriate dose of intravenous neostigmine (0.05mg/kg) and glycopyrrolate (0.01mg/kg). Extubation was performed when respiration became adequate in tidal volume and patient was able to obey simple commands e.g. open the eyes and head lift. All patients were administered oxygen therapy in post anesthesia care unit and severity of pain along with hemodynamic parameters were assessed immediately postoperatively (after extubation) and thereafter every hour till 2 hours and 2 hourly for the period of 12 hours postoperatively.

Before induction of anaesthesia, patients were instructed on how to use a 100-cm visual analogue scale (VAS), with anchors ranging from 'no pain' to 'worst possible pain', and verbal rating scale (VRS) for pain, with the following scores: 0 = no pain and patient sedated, 1 = patient awake and no pain on coughing, 2 = pain on coughing but not on deep breathing, 3 = pain on deep breathing but not at rest, 4 = slight pain at rest and 5 = severe pain at rest.

Patients were transferred to post anesthesia care unit to monitor any post operative pain. The degree of postoperative pain were assessed using VAS in case of spontaneous pain and VRS upon patient's arrival in the recovery room.



Rescue analgesic intravenous tramadol 100mg was given to patients with VAS ≥ 40 and or VRS ≥ 3 and duration of analgesia was calculated from time of extubation to time of first analgesic requirement. Patients were regularly asked about pruritis and shoulder pain, blood pressure was regularly monitored for episodes of hypotension, heart rate was regularly monitored for episodes of bradycardia. Total duration of surgery was recorded for all cases.

Statistical Analysis was done using Microsoft Excel and SPSS software (version 23.0). Categorical data was compared using Chi square test, parametric/numerical data was compared using one way ANOVA and repeated measure ANOVA and non-parametric/ordinal data was compared using Mann Whitney U test. P value < 0.05 was considered statistically significant, P value < 0.001 was considered highly significant.

RESULTS

Demographic data was comparable between both groups (p>0.05). In present study, the majority of patients were middle-aged in both the groups. The mean height, mean weight and duration of surgery in either group were also identical. (Table 1)

Table 1: Demographic profile

	Group I (N=53)	Group II (N=53)	P value
Age (years)	41.96±9.84	43.30±9.96	0.488
Height (cm)	161.21±5.3	163.11±6.36	0.098
Weight (kg)	64.55±7.46	66.79±7.39	0.123
Sex (M:F)	34:19	28:25	0.324
ASA(Grade I:Grade II)	11:42	9:44	0.804
Duration of surgery (mins)	60.64 ± 4.77	62.09 ± 4.46	0.109

Data are presented in Mean + SD or absolute numbers; * P value <0.05 is statistically significant and **P value <0.001 is highly significant statistically

VAS SCORE

In the present study, Mean VAS and median VAS scores were significantly lower in group ropivacaine plus fentanyl than group Ropivacaine only during all time intervals. The statistical variation in the mean verbal rating scale (VRS) between the two groups of patients was significant immediately after extubation and at 1st hour and from 2nd hour upto 12th hour post operatively was statistically highly significant (p<0.001). Median VRS of both groups was found to be statistically highly significant (P<0.001) at all time intervals i.e. from immediately after extubation to 12th postoperative hour. (Table 2,3,,4,5)

Table 2: Mean visual analogue scale (VAS)

Time interval	Group I (N=53)	Group II (N=53)	*P value
	Mean ± SD	Mean ± SD	
Immediate after extubation	22.87±4.87	21.30±6.16	0.190
1st postoperative hour	27.42±7.48	24.71±7.31	0.062
2nd postoperative hour	32.92±6.11	27.82±6.52	<0.001**
4th postoperative hour	15.28 ± 6.33	10.02±6.23	<0.001**
6th postoperative hour	22.11±1.35	20.46 ±0.10	<0.001**
8th postoperative hour	30.13±1.05	26.32±0.71	<0.001**
10th postoperative hour	28.42±1.06	23.22±0.56	<0.001**
12th postoperative hour	22.81±2.03	18.40±0.95	<0.001**

Data are presented in Mean + SD or absolute numbers;*P value <0.05 is statistically significant and **P value <0.001 is highly significant statistically

Table 3: Median visual analogue scale (VAS)

Time interval	Group I (N=53)	Group II (N=53	*P value
	Median	Median	

Immediate after extubation	22.17	21.51	0.133
1st postoperative hour	27.20	24.30	0.087
2nd postoperative hour	33.77	29.91	0.002*
4th postoperative hour	15.32	10.19	<0.001**
6th postoperative hour	21.99	21.59	0.412
8th postoperative hour	30.13	26.24	<0.001**
10th postoperative hour	28.15	23.27	<0.001**
12th postoperative hour	22.91	18.20	<0.001**

Data are presented in Mean + SD or absolute numbers;*P value <0.05 is statistically significant and **P value <0.001 is highly significant statistically

Table 4: Mean verbal rating scale (VRS)

Time interval	Group I (N=53)	Group II (N=53)	*P value
	Mean±SD	Mean±SD	
Immediately after extubation	1.84±0.43	1.62±0.31	0.002*
1st postoperative hour	2.06±0.59	1.74±0.33	0.001*
2nd postoperative hour	2.52±0.09	1.99±0.01	<0.001**
4th postoperative hour	1.20±0.06	1.02±0.05	<0.001**
6th postoperative hour	1.91±0.08	1.70±0.06	<0.001**
8th postoperative hour	2.12±0.06	1.64±0.06	<0.001**
10th postoperative hour	1.65±0.08	1.14±0.07	<0.001**
12th postoperative hour	1.20±0.05	1.0±0.01	<0.001**

Data are presented in Mean + SD or absolute numbers;*P value <0.05 is statistically significant and **P value <0.001 is highly significant statistically

Table 5: Median verbal rating scale (VRS

Time interval	Group I (N=53)	Group II (N=53)	*P value
	Median	Median	
Immediately after extubation	1.81	1.62	<0.001**
1st postoperative hour	2.02	1.85	<0.001**
2nd postoperative hour	2.50	2.00	<0.001**
4th postoperative hour	1.21	1.02	<0.001**
6th postoperative hour	1.91	1.71	<0.001**
8th postoperative hour	2.12	1.65	<0.001**
10th postoperative hour	1.65	1.15	<0.001**
12th postoperative hour	1.20	1.00	<0.001**

Data are presented in Mean + SD or absolute numbers;*P value <0.05 is statistically significant and **P value <0.001 is highly significant statistically

Time to requirement of first-dose rescue analgesia in our study was longer in group Ropivacaine plus fentanyl (164.10±15.26min) than in group Ropivacaine only (136.57±13.20), indicating better and longer pain relief in patients receiving ropivacaine plus fentanyl compared with patients receiving ropivacaine alone. Total analgesic consumption (tramadol) was also significantly lower in group Ropivacaine plus fentanyl (103.78±10.04mg) than group Ropivacaine only (141.09±10.29mg).(Table 6)

Table 6: Analgesic consumption of the studied patients

Variables	Group I (N=53) Mean±SD	Group II (N=53) Mean±SD	P value
Time to 1st analgesic requirement (min) (Duration of analgesia)	136.57±13.20	164.10 ±15.26	<0.001**
Total analgesic consumption (mg)	141.09 ±10.29	103.78 ± 10.04	<0.001**

Data are presented in Mean + SD or absolute numbers; *P value <0.05 is statistically significant and **P value <0.001 is highly significant statistically

Haemodynamic parameters were stable and comparable in both groups. Incidences of side effects eg pruritis, emesis, hypotension bradycardia and shoulder pain were comparable in both groups. Incidence of adverse effects in both groups was done using chi square test and depicted in the table 7.

Table 7: Incidence of adverse effects in both groups

Adverse effects	Group I (N=53)	Group II (N=53)	*P value
Pruritus	0 (0%)	3 (6%)	0.166
Emetic Symptoms	3 (5.6%)	2 (3.8%)	0.646
Hypotension	1 (1.9%)	2(3.8%)	0.558
Bradycardia	1 (1.9%)	3(5.7%)	0.308
Shoulder pain	0 (0%)	0 (0%)	---

Data are presented in Mean + SD; *P value <0.05 is statistically significant and **P value < 0.001 is highly significant statistically

DISCUSSION

Combining intraperitoneal local anaesthetics with opioids after laparoscopic cholecystectomy provides additional analgesic benefit has been proved with various previous studies. The presence of inflammation has been found to enhance the efficacy of peripherally applied opioids. This is because inflammation disrupts the perineurium as well as increases the number of peripheral sensory nerve terminals.4 The addition of opioids to local anaesthetics for postoperative pain, results from a truly peripheral rather than a central site of action. It has been postulated that inflammatory hyperalgesia is especially amenable to peripheral antinociception.[4,6]

Ropivacaine (l-propyl-2', 6'-pipecoloxylidide hydrochloride) is a long-acting amide local anesthetic that is formulated as the pure S-enantiomer, has been shown to be less toxic to cardiac and central nervous system. This drug possesses anti-inflammatory activity that may further reduce pain when administered locally. The reason of preferring ropivacaine in our study is that it is a long-acting agent (6-12 hours), has less motor blockage and a less cardiotoxicity than bupivacaine.7 Kucuk C et al in their study have shown that in preventing postoperative pain 150 mg of ropivacaine was significantly more effective than 100 mg of bupivacaine and 100 mg

of ropivacaine.8 Meena RK et al in their study concluded that analgesia provided by ropivacaine is of longer duration as compared to bupivacaine[9]

Fentanyl is a short acting opioid which is a μ-receptor agonist which in present study is used in combination with Ropivacaine. Administration of lipophilic opioid (Fentanyl) in the peritoneal cavity provides better analgesia. Fentanyl with its less histamine releasing property and a stronger μ receptor agonist activity is a better drug for peripheral analgesia. Evidence has shown that fentanyl may have dual mechanism of action, being an opioid of phenolpiperidine group it could have local anesthetic effect on the nerves and the fentanyl induced enhancement of postoperative analgesia is mediated by peripheral opioid receptors.[10,11]

Bahram MAL et al compared the effectiveness of intraperitoneal ropivacaine instillation with IM tramadol for postoperative pain relief after laparoscopic cholecystectomy and concluded that intraperitoneal ropivacaine instillation reduced postoperative abdominal and shoulder pain significantly in comparison to IM tramadol. Rescue analgesic doses were also significantly low with intraperitoneal ropivacaine.[12]

A Singh et al in their study concluded that the combination of intraperitoneal ropivacaine and fentanyl is superior to plain ropivacaine for reducing postoperative pain in patients who underwent laparoscopic surgery, without any significant increase in adverse events. It prolongs duration of pain relief reduces not only the intensity of visceral, parietal, and shoulder pain but also the total rescue analgesic dose consumption. VAS and VRS scores were significantly lower in group ropivacaine plus fentanyl as compared to group Ropivacaine. Blood pressures (systolic, diastolic, and mean) were comparable and statistically insignificant in all three study groups, the reason being the rescue analgesia given on demand whenever VAS scores reached 40. The incidence of emesis was comparable in group Ropivacaine and fentanyl (6%) and group Ropivacaine (6%) and concluded that ropivacaine instillation reduces the incidence of nausea and vomiting. They observed that the incidence of hypotension (0% vs 6%) and bradycardia (2% vs 18%) was higher in group ropivacaine with fentanyl as compared to ropivacaine alone.[13]

Gupta R et al in their study concluded that 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.[14]

CONCLUSION

Intraperitoneal instillation of local anaesthetic is an easy, cheap and noninvasive method that provides good analgesia in the postoperative period after laparoscopic surgery. Ropivacaine with fentanyl reduces not only the intensity of pain but also the total dose of rescue analgesic consumption. Better and longer pain relief is attained by using fentanyl with ropivacaine as compared to ropivacaine alone. Therefore, this study concludes that intraperitoneal instillation of ropivacaine with fentanyl reduces not only the intensity of visceral, parietal and shoulder pain but also the total rescue analgesic dose consumption.

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