

## EVALUATION OF POST OPERATIVE ANALGESIC EFFECTS OF INTRAPERITONEAL INSTILLATION OF BUPIVACAINE WITH MORPHINE VERSUS BUPIVACAINE WITH BUPRENORPHINE FOR LAPAROSCOPIC CHOLECYSTECTOMY : A DOUBLE BLIND COMPARATIVE STUDY

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### Abstract

**Background:** Local anaesthetic instillation along with opioid into the peritoneum has good outcome in terms of relieving pain in post operative period after Laparoscopic cholecystectomy. **Aims and Objectives:** To assess, compare and evaluate post operative analgesic effects of intraperitoneal instillation of 25ml 0.25%Bupivacaine and 2mg Morphine versus 25ml 0.25%Bupivacaine and 0.3mg Buprenorphine to provide effective post operative pain relief in patients undergoing Laparoscopic cholecystectomy under general anaesthesia. **Study design:** This was a prospective, randomized, double-blind study. **Materials and Methods:** After obtaining ethical committee's clearance and informed consent, sixty patients, aged between 18-60 years, of either gender belonging to American Society of Anesthesiologists physical status I & II scheduled for Laparoscopic cholecystectomy were included and categorized into two groups (n = 30). Group BM received 25 mL 0.25% Bupivacaine+2mg Morphine diluted with 0.8ml saline and Group BB received 25mL of 0.25% Bupivacaine+0.3mg Buprenorphine intraperitoneally after surgery. Total volume of 26ml anaesthetic solution was used in both groups. **Statistical analysis:** The data were analyzed using paired t-test. The results were analyzed and compared to previous studies. SPSS software version 22 was used. **Results:** Buprenorphine and Morphine along with Bupivacaine prolonged the duration of post-operative analgesia. Haemodynamic stability and side effects with both opioids were statistically insignificant. The VAS score is less in group BB as compared to group BM and was statistically significant (p<0.05) at 30min, 1hr, 2hr, 4hr, 8hr, 12hr i.e 0,1,1,1,1,2. **Conclusion:** Buprenorphine and Morphine were found to be safe adjuvants but the analgesic requirements in patients undergoing laparoscopic cholecystectomy was less when Buprenorphine with Bupivacaine was instilled intraperitoneally as compared to patients who received Morphine with Bupivacaine.

## INTRODUCTION

The word pain is derived from "Poena", Greek word meaning penalty or punishment. The International Association for the Study of Pain defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."<sup>[1]</sup> Inflammation due to tissue trauma (i.e. surgical incision, dissection, burns) or direct nerve injury (i.e. nerve transection, stretching, or compression) results in

pain. Although, laparoscopic approach of removal of gall bladder is minimally invasive surgery, the pain due to visceral nociceptors stimulation is the concern for ambulating the patient in early post operative period.<sup>[2]</sup>

Pain in laparoscopic cholecystectomy is due to three components, visceral, parietal and referred shoulder pain. Distension of peritoneum rapidly, intraperitoneal inflammation, traction of neurovascular structures, diaphragmatic irritation may result in pain in Laparoscopic cholecystectomy.

The enteric nervous system carrying this pain signal includes vast network of distinct and functionally diverse neuronal subtypes.<sup>[3]</sup> Viscera such as gall bladder and peritoneum carry unpleasant sensations and autonomic response to injury through afferents in vagus nerve called nociceptors.<sup>[4]</sup> The fact that pain is due to several components, alleviating pain postoperatively discharging the patient within a reasonable time, continues to be a challenge.

Recently peripheral use of local anesthetics for postoperative pain relief has gained popularity. Combination of intraperitoneal local anaesthetic with many opioids have been studied in the past.<sup>[5]</sup>

A simple, economical method to alleviate pain is intraperitoneal instillation with local anaesthetics (bupivacaine) with opioids (morphine, buprenorphine) etc.

The present study is aimed at comparing Bupivacaine with opioids as agents for pain relief by intraperitoneal instillation of local anesthetics in patients after laparoscopic cholecystectomy. The aim of our study was to determine

1. Duration of post operative analgesic effect of 0.25% Bupivacaine+2mg Morphine and 0.25% Bupivacaine+0.3mg Buprenorphine
2. Haemodynamic changes following intraperitoneal instillation of the above mentioned drugs and need of rescue analgesia
3. Any side effects or complications.

## MATERIALS AND METHODS

After obtaining approval and clearance from Institutional Ethical Committee, patients aged between 18 year and 60 year belonging to American Society of Anaesthesiology (ASA) I and II and also who are willing to give informed written consent were included in the study.

Pre anesthetic examination was done and standard NPO guidelines were followed. Premedication with inj. pantaprazole 40mg i.v, inj. ondansetron 4mg was given

Patients were randomized into two groups i.e BM and BB group.

BM group received intraperitoneal instillation of 26ml 0.25% Bupivacaine + 2mg Morphine and BB group received intraperitoneal instillation of 26ml 0.25% Bupivacaine + 0.3mg Buprenorphine. The drug solution was prepared by the doctor who does not participate in the study.

A standardized general anaesthetic regime was employed consisting of Inj. Glycopyrrolate 0.005 mg/kg IV, Inj. Midazolam 0.05mg/kg IV, Inj. Fentanyl 0.002mg/kg IV and Inj. Propofol 2 mg/kg IV with muscle relaxant Inj. Vecuronium bromide 0.1mg /kg to facilitate smooth direct laryngoscopy and endotracheal intubation. Anaesthesia was maintained by 33% oxygen, 66% nitrous oxide, Isoflurane at 1 MAC and muscle relaxation by intravenous vecuronium bromide 0.01mg/kg in regular bolus doses. Mechanical ventilation was

provided in control mode maintaining end-tidal CO<sub>2</sub> between 30- 40 mmHg and SpO<sub>2</sub> between 96-100%.

All patients underwent standard four port Laparoscopic cholecystectomy performed by experienced Laparoscopic surgeons. Pneumoperitoneum was created using carbon dioxide and was maintained at pressure between 12 to 14 mm Hg.

After removal of gall bladder, haemostasis was achieved and the peritoneal cavity was given thorough wash and suctioning was done. The Laparoscopic surgeon was requested to instill either of the drug solution (BM or BB) into gallbladder area, upper surface of liver and into space near and above the hepatoduodenal ligament through the epigastric port before closure of skin. If surgical drain is put, then the surgeon was requested to occlude the drain for one hour for absorption of the instilled solution into peritoneal cavity.

Patients in each group were monitored for electrocardiogram (ECG), heart rate, oxygen saturation (SpO<sub>2</sub>), non-invasive blood pressure (NIBP) and end tidal carbon dioxide (ETCO<sub>2</sub>).

Post operative pain was evaluated using Visual Analog scale (pain score 0 – 10) for 24hr after surgery. The post operative pain outcome was reported at 0 and 30 min, 1hr, 4hr, 12hr, 16hr, 20hr, 24hr. The cut off value for VAS is 4 for indication of rescue analgesic. At VAS  $\geq$ 4, rescue analgesics was administered on request by inj. Diclofenac 75mg intramuscular postoperatively

Adverse effects (nausea, vomiting, pruritis) if any were noted.

### Statistical Analysis

The data was systemically collected, compiled and statistically analyzed to draw relevant conclusions. The above mentioned parameters and patients characteristics were compared using appropriate statistical results. The data was analyzed using paired t-test. The p value was determined finally to evaluate the levels of significance.  $p > 0.05$  was considered insignificant and  $p = 0.01-0.05$  was considered significant. The results were analyzed and compared to previous studies. SPSS software version 22 was used.

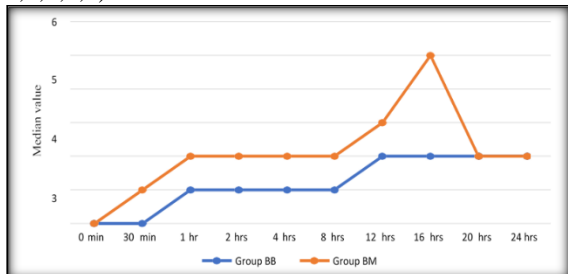
## RESULTS

The two groups were similar for age, weight, duration of surgery and type of operative procedures.

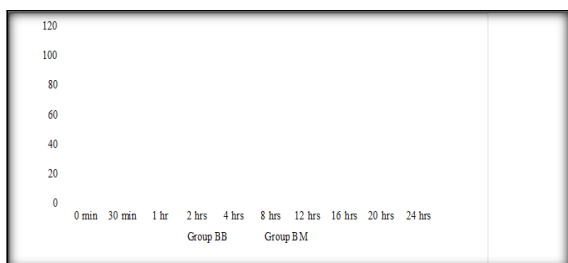
Intraperitoneal instillation of Morphine (2mg) or Buprenorphine (0.3mg) with Bupivacaine (0.25% 25ml) significantly reduces immediate post operative pain (figure 1). The VAS score is less in group BB as compared to group BM and was statistically significant ( $p < 0.05$ ) at 30min, 1hr, 2hr, 4hr, 8hr, 12hr i.e 0,1,1,1,1,2 (table 1)

Total analgesic consumption was less in group BB as compared to group BM. The incidence of nausea

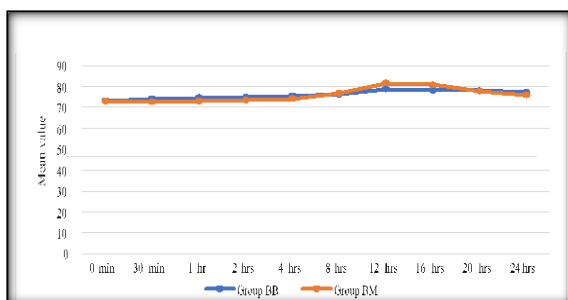
and vomiting was similar and there was no significant difference among the two groups. The present study shows that there is no haemodynamic variations i.e systolic blood pressure, diastolic blood pressure, heart rate ,oxygen saturation(SBP,DBP,HR,SpO2) between the two groups i.e statistically insignificant( $p>0.05$ )(table 2,3,3,4,5).



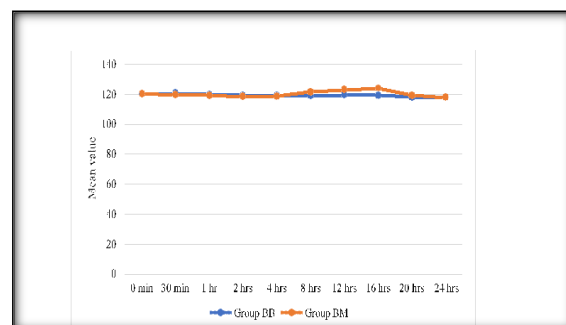
**Figure 1: Comparison of VAS score between two group**



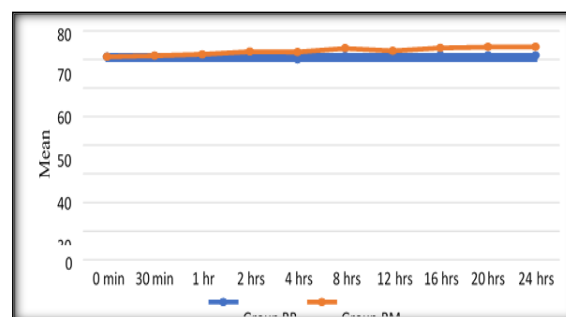
**Figure 2: Comparison of median SpO2 score between two groups**



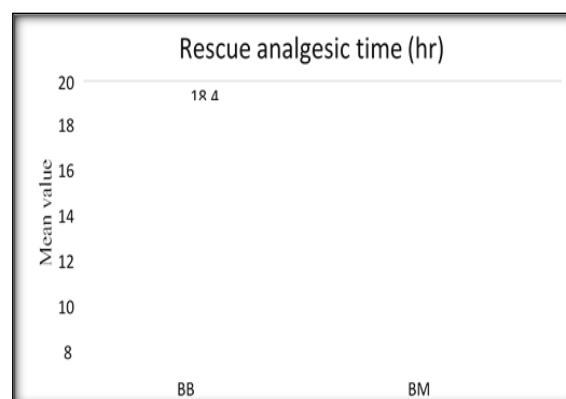
**Figure 3: Comparison of mean heart rate between two group**



**Figure 4: Comparison of mean systolic blood pressure between two group**



**Figure 5: Comparison of mean diastolic blood pressure between two group**



**Figure 6: Comparison of rescue analgesic time between two group**

**Table 1: Comparison of median VAS score between two group**

VAS	Group BB	Group BM	Unpaired t test P value
0 min	0 (0, 0)	0 (0, 0)	0.508
30 min	0 (0, 1)	1 (1, 2)	<0.001
1 hr	1 (0, 1)	2 (1, 2)	<0.001
2 hrs	1 (0, 1)	2 (1, 2)	<0.001
4 hrs	1 (0, 1)	2 (1, 2)	<0.001
8 hrs	1 (1, 2)	2 (2, 3)	<0.001
12 hrs	2 (1, 2)	3 (2, 6)	<0.001
16 hrs	2 (1, 2.25)	5 (2, 6)	0.581
20 hrs	2 (1, 2.25)	2 (1.25, 2)	0.853
24 hrs	2 (1, 2.25)	2 (1, 2)	0.037

**Table 2: Comparison of SpO2 between two group**

SPO2	Group BB	Group BM	Unpaired t test P value
0 min	100 (99, 100)	100 (99, 100)	0.806
30 min	99 (99, 100)	100 (99, 100)	0.123
1 h	99 (99, 100)	99 (99, 100)	0.366
2 hr	99 (99, 100)	100 (99, 100)	0.184
4 hr	99 (99, 100)	100 (99, 100)	0.088
8 hr	99 (99, 100)	99.50 (99, 100)	0.117
12 hr	99 (99, 100)	99 (99, 100)	0.605
16 hr	99 (99, 100)	99 (99, 100)	0.595
20hr	99(99,100)	100(99,100)	0.124
24hr	100(99,100)	100(100,100)	0.128

**Table 3: Comparison of mean heart rate between two group**

Heart Rate	Group BB	Group BM	Unpaired t test P value
0 min	73.23 ± 7.67	72.97 ± 7.60	0.893
30 min	74.13 ± 6.48	72.70 ± 5.75	0.369
1 hr	74.63 ± 6.07	73.10 ± 4.62	0.275
2 hrs	74.97 ± 5.80	73.53 ± 3.99	0.270
4 hrs	75.47 ± 5.63	74.20 ± 4.27	0.330
8 hrs	76.27 ± 5.82	76.83 ± 4.62	0.678
12 hrs	78.70 ± 8.08	81.63 ± 5.18	0.100
16 hrs	78.17 ± 6.37	80.70 ± 5.10	0.094
20 hrs	77.90 ± 6.57	77.87 ± 4.34	0.982
24 hrs	77.20 ± 6.04	75.97 ± 4.35	0.368

**Table 4: Comparison of mean systolic blood pressure between two group**

SBP	Group BB	Group BM	Unpaired t test P value
0 min	73.23 ± 7.67	72.97 ± 7.60	0.893
30 min	74.13 ± 6.48	72.70 ± 5.75	0.369
1 hr	74.63 ± 6.07	73.10 ± 4.62	0.275
2 hrs	74.97 ± 5.80	73.53 ± 3.99	0.270
4 hrs	75.47 ± 5.63	74.20 ± 4.27	0.330
8 hrs	76.27 ± 5.82	76.83 ± 4.62	0.678
12 hrs	78.70 ± 8.08	81.63 ± 5.18	0.100
16 hrs	119.33 ± 11.78	123.87 ± 6.66	0.072
20 hrs	118.00 ± 10.24	119.27 ± 5.21	0.548
24 hrs	117.73 ± 10.67	117.87 ± 4.23	0.949

**Table 5: Comparison of mean diastolic blood pressure between two group**

DBP	Group BB	Group BM	Unpaired t test P value
0 min	71.00 ± 6.92	71.00 ± 6.92	1.000
30 min	71.20 ± 7.64	71.40 ± 5.54	0.908
1 hr	70.87 ± 6.78	71.87 ± 5.06	0.520
2 hrs	70.93 ± 7.29	72.80 ± 4.54	0.239
4 hrs	70.07 ± 7.31	72.67 ± 3.80	0.089
8 hrs	71.33 ± 8.44	73.93 ± 4.38	0.140
12 hrs	70.70 ± 7.76	73.07 ± 3.18	0.142
16 hrs	71.57 ± 8.25	74.13 ± 3.71	0.125
20 hrs	71.53 ± 8.63	74.40 ± 3.50	0.097
24 hrs	71.47 ± 8.88	74.47 ± 4.19	0.100

**Table 6: Comparison of mean rescue analgesic time between two group**

	Group BB	Group BM	Unpaired t test P value
Rescue analgesic time (hr)	18.40 ± 4.56	14.00 ± 2.52	0.003

**Table 7: Comparison of side effects between two group**

Side effects	Group BB	Group BM
Nausea	3 (10%)	3 (10%)
Vomiting	26 (86.7%)	26 (86.7%)
Nil	26 (86.7%)	26 (86.7%)
Total	30 (100%)	30 (100%)

## DISCUSSION

Laparoscopic surgeries are popularized for their small incision, shorter hospital stay and early ambulation. The origin of pain after laparoscopic cholecystectomy is multifactorial and complex in nature. It has parietal(abdominal wall)

,visceral(intra-abdominal) and referral(shoulder tip) components and analgesia provided should be multimodal. Various methods are used to alleviate pain-  
a.parenteral analgesics

- Local infiltration with local anesthetics

- Epidural and intrathecal opioids and local anesthetics
- Transverse abdominis block

Intraperitoneal local anesthetic (IPLA) have been used as “visceral blocks” since 1950 and instillation of local anaesthetics reduce shoulder tip pain, overall pain and hospital stay. Recently instillation of local anesthetics for postoperative pain relief has become a popular practice after Laparoscopy surgery.

Intraperitoneal instillation of 25ml of 0.25% Bupivacaine provides effective analgesia with plasma concentration below toxic levels (0.92 – 1.14mcg/ml). Narchi et al showed that instilling 100mg of Bupivacaine intraperitoneally did not cause toxicity.<sup>6</sup> We chose Bupivacaine 62.5mg for our study because of its potency and prolonged duration of action. Its half-life is between 5 and 16hr.

We chose the intraperitoneal route to block the visceral afferent signalling and modify visceral nociception. The local anesthetic inhibits nociception by

blocking voltage gated Na<sup>+</sup> channels and thereby inhibiting action potentials in nociceptive fibers and so block the transmission of pain impulses. They also inhibit prostaglandins and other agents that sensitize or stimulate the nociceptors and contribute inflammation.<sup>[7]</sup> The local anesthetics have anti-inflammatory actions and mechanisms of these effects may be prostaglandin antagonism, inhibition of leukocyte migration and lysosomal enzymes release, all effects seen in vitro and animal studies.

Meta analysis by Kahokehr on intraperitoneal instillation using local anaesthetic for laparoscopic cholecystectomy revealed an overall reduction of pain, opioid analgesia use, need for rescue analgesia, postoperative cortisol and glucose response.<sup>[8]</sup> Adjuvants like opioids Morphine 2mg, Buprenorphine 0.3mg has been used to potentiate the action of local anesthetic. The VAS score in Buprenorphine group was statistically less and time to rescue analgesic was 18+/-hr as compared to Morphine group i.e 14+/-2hr. This may be due to the intact peritoneum preventing the entry of hydrophilic morphine molecules and blocks their access to the neural receptors. Inflammation disrupts the peritoneal barrier and consequently the access of opioid agonists to the sensory neurons is facilitated producing analgesia only in swollen tissue.<sup>[9]</sup> Since Buprenorphine is a lipophilic opioid, it can provide better analgesia. Administration of lipophilic opioid (fentanyl or buprenorphine) in the peritoneal cavity provides better analgesia.<sup>[10]</sup>

Among the two treatment groups significant difference in pain scores exists at 30min, 1hr, 2hr, 4hr, 8hr, 12hr.

Chundrigar et al and Szem et al in their study using Bupivacaine for intraperitoneal instillation for post operative pain in patients undergoing laparoscopic cholecystectomy showed results with mean duration

of analgesia lasting 2 – 8hr only.<sup>[11,12]</sup> Malhotra et al found that 100mg of intraperitoneal instillation of bupivacaine following laparoscopic cholecystectomy provides pain relief for a longer duration (8hr) compared to 50mg of drug (4 – 6hr).<sup>13</sup> Bina et al in their study with morphine 2mg and bupivacaine 0.25% for laparoscopic gynaecological surgeries used intraperitoneal instillation with no side effects.<sup>[14]</sup> Sandeep et al instilled buprenorphine 0.3mg with bupivacaine 0.25% intraperitoneally for laparoscopic cholecystectomy surgeries as a method of post-operative analgesia with no side effects.<sup>[15]</sup> In our study, during the first 8hr analgesic requirement was significantly low in both groups. The overall analgesic requirement in BB group was less with haemodynamic stability.

Regarding adverse effects, only nausea and or vomiting was there in 8 out of 60 patients and was equally distributed in all groups. There was no pruritis, excessive sedation or dryness of mouth in both group patients. This may be explained as the dose of morphine and buprenorphine used in our study for intraperitoneal instillation was significantly less to produce systemic side effects. Vital parameters like HR, BP and SpO<sub>2</sub> are important indicators of patient comfort as the values correlated well with high scores.

## CONCLUSION

Intraperitoneal instillation of local anesthetics and opioid is an easy, economical and non-invasive method which provides good analgesia in the postoperative period after Laparoscopic surgery. The combination of intraperitoneal instillation of Bupivacaine with Buprenorphine is superior to Morphine with Bupivacaine for the relief of postoperative pain in patients undergoing Laparoscopic cholecystectomy without any significant adverse effects. This peripheral action of opioid particularly in inflamed tissue provides support for the existence of peripheral opioid receptors and gives a new approach to pain management which may have great clinical benefits. From the present study we conclude that although, RBC indices and histograms obtained by hematology analyzer give valuable inputs, but peripheral blood smear examination still remains the gold standard in categorization of various types of anemia as they provide additional morphological details which cannot be interpreted by mere numerical data provided by automated analyzers. RBC indices and histograms can guide as to which cases peripheral examination can be restricted to, thus increasing efficiency and reducing the workload in the laboratory. Both tests are complementary to each other and an integrated approach is advocated.

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Conflicts Of Interest None

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