e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(11); 72-79

Original Research Article

# Study the Comperative Outcome of Postoperative Analgesic Effect of Intraperitoneal Bupivacaine with Fentanyl and Bupivacaine with Nalbuphine in Laparoscopy Cholecystectomy

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**Received: 20-08-2022 / Revised: 25-09-2022 / Accepted: 30-10-2022**

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**Conflict of interest: Nil**

**Abstract**

**Aim:** The aim of the study was to compare the effectiveness of intraperitoneal bupivacaine with fentanyl and intraperitoneal bupivacaine with nalbuphine for postoperative pain relief after laparoscopic cholecystectomy.

**Methods:** The randomized, prospective, double-blinded, intervational clinical study was carried out in an IGIMS Patna hospital, over 1 year time after obtaining the necessary approval from the Institutional ethical committee. 80 patients were included in the present study. Selected patients were allocated to two groups, each containing 40 patients – Group BF (n = 40) were given 18 mL of 0.5% bupivacaine combined with 1 µg/kg fentanyl diluted with normal saline making total volume 20 ml and Group BN (n = 40) were given 18 mL of 0.5% bupivacaine combined with 2mg nalbuphine making total volume 20 ml through trocars i.e the total volume were 20 ml.

**Results:** Eighty patients, scheduled for laparoscopic cholecystectomy, were entered into the study. Demographic data of patients and duration of surgery showed no considerable difference (p-value >0.05). The number of female patients was more in both the groups, but it was statistically insignificant. The two groups were comparable in terms of duration of surgery as well but not significant (p-value >0.05). VAS score at rest showed significant difference (favourable score in nalbuphine group) at one hour postextubation. At all the other time frames, the difference in VAS score was insignificant.

**Conclusion:** Intraperitoneal instillation of bupivacaine in combination with nalbuphine significantly reduces postoperative pain scores in comparison to bupivacaine with fentanyl, in patients undergoing ambulatory laparoscopic cholecystectomy.

**Keywords:** Analgesia, Rescue analgesic, Visual analog scale score on movement, Visual analog scale score at rest

## Introduction

Laparoscopic cholecystectomy (LC) is the most accepted surgical technique for cholelithiasis as compared to open cholecystectomy. Laparoscopic procedures have many advantages over open procedures such as lesser haemorrhage, better cosmetic results, lesser postoperative pain and shorter recovery time leading to a shorter hospital stay and less expenditure. [1]

Laparoscopic cholecystectomy is widely performed, and it has replaced open cholecystectomy as the gold standard for cholelithiasis. Laparoscopic surgeries are favored over open surgeries because they have a number of advantages such as reduced postoperative pain and analgesic requirement, improved postoperative respiratory function, rapid return of gastrointestinal function, a reduced stress response to surgery and recovery time, less postoperative wound infection, and improved cosmetic appearance. [2-4]

Postoperative pain is an important factor contributing to patient morbidity during recovery. After laparoscopic cholecystectomy, pain can arise from the incision site (somatic pain), visceral structures (visceral pain) [5], and shoulder tip (referred pain from the sub diaphragmatic region). Visceral pain occurs due to the stretching of the parietal peritoneum, the release of inflammatory mediators of pain, and the irritation produced by blood. Referred shoulder pain is often mild and is due to the irritation of the diaphragm by residual gas. [6]

The stretching of intra-abdominal cavity [7], peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide [8,9] in peritoneal cavity, leads to pain in upper and lower abdomen, back and shoulder region. The afferents of the vagus nerve transmit unpleasant sensations from various visceral organs and their peritoneum, like gall bladder. These are the silent nociceptors and they get activated by intraperitoneal inflammation and injury, and hence give rise to painful and nonpainful sensations.

The rationale for using an intraperitoneal route for instilling a drug, local anaesthetic or opioid is that the exposure of peritoneum to visceral nociceptive conduction provides additional mechanism of analgesia. Hence, the need for intraperitoneal administration of local anaesthetics [10,11] or opioids [12,13] arose to induce postoperative analgesia and decrease intravenous analgesic requirements.

Nalbuphine has a unique pharmacology. Hence, it offers an advantage in pain management. It is a μ antagonist and a partial k agonist for beta-arrestin-2 G-proteins. The partial κ agonist for G-proteins and its interactions with it offers benefits such as less nausea, pruritus, and respiratory depression than morphine. [14] Bupivacaine is a long-acting local anaesthetic and has been extensively used in intraperitoneal instillation for various laparoscopic procedures. [7]

The aim of the study was to compare the effectiveness of intraperitoneal bupivacaine fentanyl and intraperitoneal bupivacaine with nalbuphine for postoperative pain relief after laparoscopic cholecystectomy. The primary outcome measures were: VAS score at different intervals at rest and at movement and to determine the time of first analgesic request. The secondary outcome measures were: to compare the Haemodynamic of both the groups and their relation to the VAS score, to compare the analgesic request rate (number of doses of tramadol in 24 hours), incidence of shoulder pain and time to return to normal activity.

## Materials and Methods

The randomized, prospective, double-blinded, intervational clinical study was carried out in an IGIMS Patna hospital,

over 1 year time after obtaining the necessary approval from the Institutional ethical committee. 80 patients were included in the present study. The informed consent was obtained from the patients.

Patients were evaluated by –

- Detailed history
- Detailed general examination
- Systemic examination
- Patient's consent was taken after explanation of procedure in their mother tongue.
- Drugs used were explained to the patient and also educated about Numerical pain scale.
- Selected patients were allocated to two groups, each containing 40 patients – Group BF (n = 40) were given 18 mL of 0.5% bupivacaine combined with 1 µg/kg fentanyl diluted with normal saline making total volume 20 ml and Group BN (n = 40) were given 18 mL of 0.5% bupivacaine combined with 2mg nalbuphine making total volume 20 ml through trocars i.e the total volume was 20 ml.
- Patients would be fasted for 6 hours before the surgery. Drug was instilled through the laparoscopic irrigation system. The study drug according to the group allocation was instilling over the gall bladder bed, hepatoduodenal ligament and hepatodiaphragmatic space by the operating surgeon who will be blind to the study drug.
- The quality of analgesia was assessed using numeric pain rating scale (NRS).

**Inclusion criteria:**

1. Age of patient between 18 to 60
2. Either sex of patient
3. ASA 1 & 2
4. Valid consent

**Exclusion criteria:**

1. patient on concomittent analgesic or sedative
2. Patient not giving consent
3. Patient allergic to study drug
4. History of seizure or myoclonus

The time of drug instilled over the gall bladder bed, hepatoduodenal ligament and hepatodiaphragmatic space to first rescue analgesia. Before inducing general anaesthesia to the patient, the visual 10 VAS (where 0 indicates no pain and 10 indicates agonising pain) was explained to every patient. The same team of surgeons performed all the surgeries. General anaesthesia was induced by the same anaesthetic protocol for both groups. It employed fentanyl 2 µg/kg for analgesia, 2 mg/kg intravenous propofol and 0.1 mg/kg injection vecuronium. Standard monitoring was done for each case (lead II and V5 ECG monitoring, non-invasive MAP measurements, EtCO2, SpO2). Minute ventilation was adjusted to keep EtCO2 at 35-45 mm Hg. Intravenous dexamethasone 8 mg was given at induction and injection ondansetron 8 mg was administered at skin closure. Maintenance was done with isoflurane (0.5-1%) and vecuronium 0.02 mg/kg as needed. Recovery was performed by discontinuation of general anaesthetics and reversal of neuromuscular blockers, and extubation was performed after ensuring adequate motor power. During laparoscopy, intra-abdominal pressure was maintained at 10-12 mm of Hg. After removal of gall bladder and before the removal of trocar, nalbuphine/local anaesthetic was instilled in Trendelenburg position in hepatodiaphragmatic space on gall bladder bed. CO2 was carefully evacuated from the peritoneal cavity at the end of the surgery.

After recovery, patients were asked to rate the pain. After which they were monitored for HR and MAP every 15 minutes during the first hour and then every four hours for 24 hours. Patients were asked to rate the intra-abdominal pain. The severity of intra-abdominal pain was assessed using VAS, IAR, after one hour and then every four hours from recovery in the first 24 hours. Intra-abdominal pain was defined as

pain inside the abdomen which is deep, dull and more difficult to localise, and may resemble biliary colic. VAS at the same intervals was also assessed on changing position from supine to lateral i.e., on movement. A 1 gm paracetamol was prescribed to be given eight hourly. Still, if VAS was more than 3, Injection diclofenac

75 mg was administered intramuscularly. On additional request by patient Injection tramadol 50 mg was given in 100 mL saline. Any complications such as shoulder pain respiratory depression, nausea, vomiting and/or itching were also recorded. The total dose of consumed analgesic (only diclofenac and tramadol) was noted.

**Statistical Analysis**

Statistical analysis was performed using SPSS version 20.0 (SPSS Ltd., Chicago, IL, USA). Continuous variables were represented as mean values with standard error or frequency. Nominal categorical data like gender, ASA-physical status were analysed using Chi-square test and ordinal data like comparison of the VAS scale and rescue analgesic dose were analysed by Mann-Whitney U test. For all determinations, p-value <0.05 (2tailed) was considered statistically significant.

**Results**

**Table 1: Demographic characteristics of patient and surgical data**

| Variables | Group BF | Group BN | p-value (Chi-square test) |
|---|---|---|---|
| | Mean±SD (n=40) | Mean±SD (n=40) | |
| Age (years) | 42.8±13.7 | 43.7±14 | 0.6024 |
| Sex M:F | 17:23 | 18:22 | 0.620 |
| Weight (kg) | 64.8±16.2 | 66.3±17.1 | 0.670 |
| Duration of surgery (min) | 80±13.3 | 79.3±11.5 | 0.8020 |

Eighty patients, scheduled for laparoscopic cholecystectomy, were entered into the study. Demographic data of patients and duration of surgery showed no considerable difference (p-value >0.05). The number of female patients was more in both the groups, but it was statistically insignificant. The two groups were comparable in terms of duration of surgery as well but not significant (p-value >0.05).

**Table 2: VAS score at rest and movement at different time intervals. IAR: Immediately after recovery**

| VAS at rest | Group BF | Group BN | p-value (MannWhitney U-test) |
|---|---|---|---|
| IAR | 3.50±0.716 | 3.33±0. 616 | 0.260 |
| 1 h | 2.88±0.791 | 2.52±0.640 | 0.025 |
| 4 h | 2.12±0.686 | 2.03±0. 577 | 0.520 |
| 8 h | 1.75±0 .670 | 1.60±0.496 | 0.255 |
| 12 h | 1.28±0.506 | 1.30±0.464 | 0.850 |
| 16 h | 1.08±0.267 | 1.13±0.335 | 0.450 |
| 24 h | 1.03±0.158 | 1.00±0.000 | 0.310 |
| **VAS at movement** | | | |
| IAR | 4.07±0.572 | 3.50±0.506 | <0.0001 |
| 1 h | 3.48±0.784 | 3.70±0.687 | 0.180 |
| 4 h | 2.70±0.687 | 2.93±0.656 | 0.125 |
| 8 h | 2.37±0.586 | 2.35±0.533 | 0.870 |
| 12 h | 1.90±0.545 | 1.85±0.533 | 0.679 |
| 16 h | 1.43±0.501 | 1.67±0.474 | 0.030 |
| 24 h | 1.18±0.385 | 1.18±0.385 | 1.00 |

Looking at the individual trend of VAS scores in both the groups, as expected there was a gradual decrease in VAS scores over time in 24 hours. VAS score at rest showed significant difference (favourable score in nalbuphine group) at one hour postextubation. At all the other time frames, the difference in VAS score was insignificant. Meanwhile on comparing VAS at movement, significantly better score was seen at immediate post reversal period and at 16 hours in BN group. The mean time of first rescue analgesic in BN group was 20.25±7.983 minutes, while in BF group it was 26.9±6.95 minutes (p-value-0.0002). Only three patients in BN group requested for an additional analgesic (tramadol), while four in BF group did the same. In BF, eight patients (20%) and in BN group, 10 (25%) patients developed shoulder pain during the 24 hour period.

**Table 3: Postoperative complications**

| Variables | Group BF | Group BN | p-value |
|---|---|---|---|
| Shoulder pain | 7 | 10 | |
| PONV | 4 | 12 | 0.2525 |
| Itching/others | 0 | 0 | |
| Total | 11 | 22 | |

Incidence of PONV and shoulder pain was greater in nalbuphine group than in bupivacaine group. PONV was successfully treated by giving injection ondansetron 8 mg i.v. once. Also, no patient from any group complained of itching or any other complication. Fourteen patients in nalbuphine group (35%) and only five patients in bupivacaine group (12.5%) developed PONV. The difference in the postoperative side effects between the two groups was not significant.

## Discussion

Laparoscopic cholecystectomy is a widely performed, common, elective procedure. Postoperative pain is comparatively less after laparoscopic cholecystectomy than after an open cholecystectomy, but it still remains a significant cause for morbidity. [15] Patient education regarding the degree of pain they may encounter, an explanation of the pain assessment tools being used and the modalities of pain treatment available, and reassurance regarding the pain they may experience can help reduce the patients' anxiety and postoperative pain incidence.

Patients undergoing laparoscopic cholecystectomy suffer considerable pain on the day of surgery, frequently requiring opioid analgesia. After laparoscopic cholecystectomy, several types of pain can arise. Parietal pain is due to the placement of trocars through the abdominal wall. It is superficial and can be located by the patient. Bupivacaine is the most common local anesthetic used intraperitoneally for postoperative pain relief because of its high potency and longer duration of action.

Various modes of analgesia have been tried to overcome postoperative pain. The techniques that can be employed for providing pain relief in Laparoscopic surgeries include surgery under sub-arachnoid block, parentral opioids and NSAIDs, Instillation of local anaesthetics intraperitoneally, etc In this modern age of surgery, intraperitoneal instillation of local anaesthetic agents has become an important measure to control post-operative pain, nausea, vomiting and reduced hospital

stay. [16 ]

This study was conducted to determine whether bupivacaine with fentanyl and bupivacaine with nalbuphine when used intraperitoneally could improve postoperative analgesia and decrease

postoperative analgesic requirement. Both the groups were comparable and showed good postoperative pain relief (visceral). VAS scores in both the groups were less than four. There was slightly better pain control in nalbuphine group at all the times (especially at four hours at rest and 16 hours during movement and coughing).

Many studies have been done to determine the effectiveness of instillation of drugs intraperitoneally and their effect on visceral pain. Their effect on postoperative analgesic requirement and pain severity has been compared. Some studies have shown that intraperitoneal local anaesthesia is effective in controlling postoperative pain [18,19], others have shown that they are not. [17] The studies, which found intraperitoneal instillation of drugs effective, have been on various drugs especially local anaesthetics and opioids. [20] The results have been conflicting as there are several factors that can influence the benefits of intraperitoneal analgesia. Few of these factors are the type of drug, its dose and concentration, subdiaphragmatic or subhepatic instillation or before or after surgery, residual CO2, degree of head down intra-abdominal pressures during the surgery. In this study, two groups of drugs from most commonly employed drug categories were selected for comparison. Nalbuphine was chosen in this regard because of its lesser incidence of causing respiratory depression, and to compare it with the already proven beneficial intraperitoneal drug. [21]

Gupta R et al., had studied the efficacy of intraperitoneal fentanyl and bupivacaine in laparoscopic surgeries [22]. They showed that intraperitoneal instillation of fentanyl (100 μg) along with bupivacaine (0.5% 20 mL) significantly reduces immediate postoperative pain (VAS: 40.1±9.8 vs 65.2±9.5; VAS: 2.2±0.4 vs 3.8±0.4). It also reduced intensity of pain even after 24 hours (VAS: 40.3±7.4 vs 50.1±7.8; VAS: 3.50±1.2 vs 4.23±0.78). The incidence of PONV was greater in patients given intraperitoneal BN than in patients given BF. In agreement with this result, Visalyaputra S et al., [23] found greater incidence of vomiting in patients given intraperitoneal morphine than in others; however, most of other studies did not find a statistical difference between patients given either intraperitoneal lidocaine or bupivacaine or opioids and the control patients with respect to the incidence of PONV. [24]

Akinci SB et al., compared the intraperitoneal and intravenous tramadol in laparoscopic cholecystectomy for postoperative analgesic action. [13] The overall VAS scores of intraperitoneal drug were significantly lower than intravenous means. In most of the studies which were done on intraperitoneal opioids, there was no significant difference with the controls in terms of shoulder pain. [25,26] This was not in concurrence with present study findings. This may be because none of these studies used intraperitoneal nalbuphine. [27]

## Conclusion

Intraperitoneal instillation of bupivacaine in combination with nalbuphine significantly reduces postoperative pain scores in comparison to bupivacaine with fentanyl, in patients undergoing ambulatory laparoscopic cholecystectomy. This study supported the proposed hypothesis that intraperitoneal bupivacaine with nalbuphine is an easy, cheap and an effective non-invasive method to provide good analgesia in the postoperative analgesia of laparoscopic cholecystectomy. Its analgesic profile is almost comparable to intraperitoneal bupivacaine with fentanyl, though having a little more unwanted side-effect than bupivacaine.

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