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Original Article

Anaesthesia Section

Intraperitoneal Bupivacaine versus Nalbuphine in Postoperative Pain Relief after Laparoscopic Cholecystectomy: A Randomised Clinical Study

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ABSTRACT

Introduction: 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.

Aim: To compare the effectiveness of intraperitoneal bupivacaine and nalbuphine for postoperative pain relief after laparoscopic cholecystectomy.

Materials and Methods: The present study was a randomised clinical study in which 80 patients underwent laparoscopic cholecystectomy, received either bupivacaine (n=40) or nalbuphine (n=40) intraperitoneally. Each patient was monitored postoperatively, as per the institution protocol. Severity of pain was assessed using the Visual Analog Scale (VAS) at rest and at movement Immediately After Recovery (IAR), after one hour and every four hours thereafter. The time to first rescue analgesic was compared. The data analysis was carried out with unpaired Student's t-test and Chi-square test using software Statistical Package for the Social Sciences (SPSS) 20.0 version.

Results: The study included 35 males and 45 females, with a mean age of 42.8±7.1 years. Both groups were well-matched demographically. There was no significant difference in the Heart Rate (HR) or Mean Arterial Pressure (MAP) between the groups postoperatively. However, VAS score was significantly lower in nalbuphine group at one hour (2.52±0.640) as compared to bupivacaine group (2.88±0.791, p=0.028), but on movement at 16 hours it was lower in bupivacaine group (1.43±0.501), as compared to nalbuphine group (1.67±0.474, p=0.030). The mean time of first rescue analgesic in nalbuphine group was 20.25±7.983 minutes, while in bupivacaine group it was 26.9±6.95 minutes (p-value-0.0002). Postoperative Nausea and Vomiting (PONV) was significantly higher with nalbuphine (35% vs 12.5%). No other significant complication was noted in either group.

Conclusion: Intraperitoneal instillation of nalbuphine is an effective and safe way to reduce postoperative pain in patients undergoing laparoscopic cholecystectomy.

Keywords: Analgesia, Nausea and vomiting, Rescue analgesic, Visual analog scale score on movement, Visual analog scale score at rest

INTRODUCTION

The conventional open method of cholecystectomy has been replaced by laparoscopic cholecystectomy as we enter the Enhanced Recovery After Surgery (ERAS) era [1]. Laparoscopic cholecystectomy results in less postoperative pain as compared to open cholecystectomy, but still it is not a pain free procedure, which is why many patients get held back from early recovery. This becomes a major hurdle in Enhanced Recovery after Surgery (ERAS) [2]. The advent of minimally invasive techniques like single port laparoscopy and transluminal endoscopic surgery to a greater extent, bypass the abdominal wall for visceral access and resection. But as the pain after laparoscopic cholecystectomy is multidimensional, the disruption of peritoneum and dissection of viscera still cause visceral nociception. Pain intensity usually peaks during the first few postoperative hours and declines over the following 2 or 3 days [3].

The stretching of intra-abdominal cavity [4], peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide [5,6] 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 non painful 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 [7,8] or opioids [9,10] 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 κ 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 [11]. Bupivacaine is a long-acting local anaesthetic and has been extensively used in intraperitoneal instillation for various laparoscopic procedures [2,4].

No study has been done comparing intraperitoneal nalbuphine and bupivacaine and their effect on postoperative analgesia. Hence, to explore this advantage of nalbuphine, it was decided to conduct a study to compare its intraperitoneal instillation with the commonly used drug (local anaesthetic), bupivacaine, and their effects on postoperative pain after laparoscopic cholecystectomy.

The aim of the study was to compare the effectiveness of intraperitoneal bupivacaine and intraperitoneal 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 haemodynamics 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

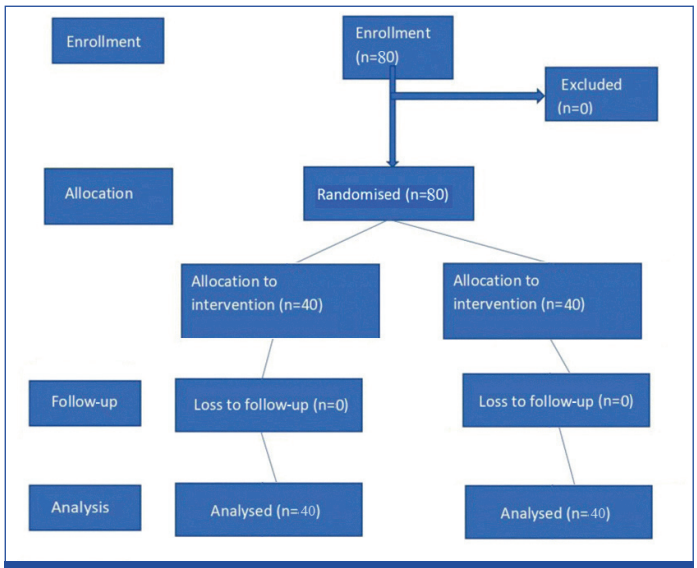
The present study was a double blind, randomised clinical study conducted over a period of nine months starting from November 2020 to August 2021. The study was conducted after approval from the Institutional Ethics Committee (IEC) (EC/NEW/INST/2020/961). The CTRI reference number is CTRI/2020/11/028869. Informed consent was taken from each patient.

Inclusion criteria: Eighty patients, American Society Of Anaesthesiologists (ASA) 1 or 2, aged 18-60 years, undergoing laparoscopic cholecystectomy were included in the study.

Exclusion criteria: Patients with history of chronic opioid intake, those with history of severe systemic disease, allergy to local anaesthetics, having obesity or pregnant females were excluded from the study. Patients those who had chronic pain diseases or had acute cholecystitis before the surgery were also excluded. When the duration of surgeries exceeded two hours, or the procedure was converted to open from laparoscopic, they were also excluded.

Sample size calculation: The sample size was calculated by taking mean±standard deviation (±11.225) and difference between the mean values of VAS 8.25 at four hours was taken from a previous study [12]. The sample size was calculated to have power of 80% with an alpha error of 0.05.

Patients were grouped randomly using computer generated series into two groups of 40 patients each. Allocation concealment was done using a sealed opaque envelope. Two groups of syringes were prepared and labelled A and B by an anaesthesia technician. Group A received 20 mL 0.5% bupivacaine and group B received 10 mg nalbuphine in 19 mL normal saline intraperitoneally [Table/Fig-1].



[Table/Fig-1]: CONSORT diagram.

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, $EtCO_2$, SpO_2). Minute ventilation was adjusted to keep $EtCO_2$ at 35-45 mm Hg. Intravenous dexamethasone 8 mg was given at induction and injection ondansetron 8 mg was administered at skin closure. Also, 1 gm paracetamol was administered intravenously towards the end of the surgery. 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. CO_2 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 (2-tailed) was considered statistically significant.

RESULTS

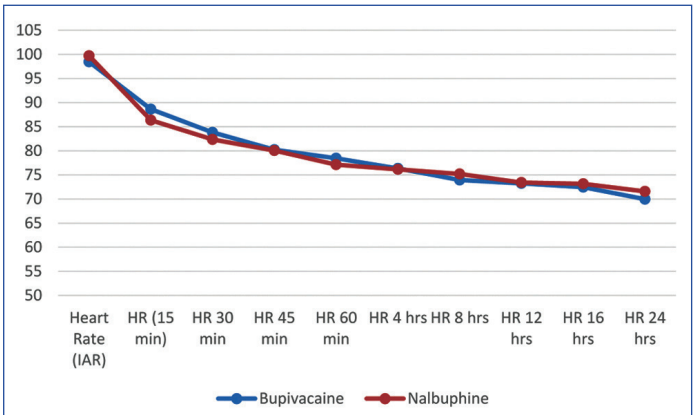
Eighty patients, scheduled for laparoscopic cholecystectomy, were entered into the study. Demographic data of patients and duration of surgery showed no considerable difference (p-value >0.05). The number of female patients was more in both the groups, but it was statistically insignificant. The two groups were comparable in terms of duration of surgery as well but not significant (p-value >0.05) [Table/Fig-2].

Variables	Mean±SD (n=40) Bupivacaine group	Mean±SD (n=40) Nalbuphine group	p-value (Chi-square test)
Age (years)	41.6±13.3	43.2±14	0.6017
Sex M:F	17:23	18:22	0.633
Weight (kg)	64.8±16.2	66.3±17.1	0.688
Duration of surgery (min)	80±13.3	79.3±11.5	0.8019

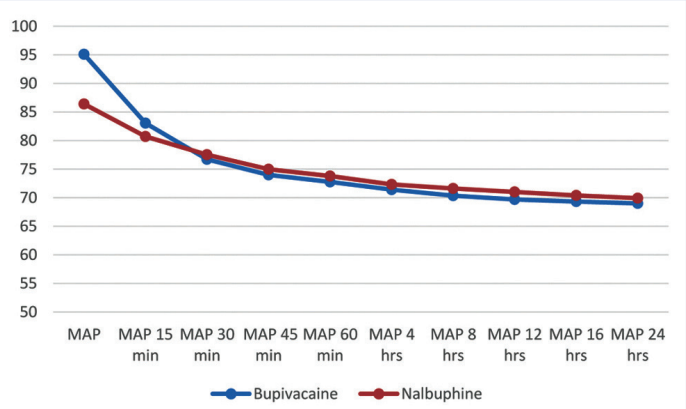
[Table/Fig-2]: Demographic characteristics of patient and surgical data.

The heart rate variations at different time intervals in both the groups was not significant, with gradual fall over the progressive time frames, with steepest fall over the first 15 minutes in both the groups, hence comparable in both the groups (mean HR group A=90.38±5.67 (beats per minute (bpm); group B=88.96±4.83 bpm; p-value=0.2311). The mean arterial pressure was also comparable in both the groups. (mean for bupivacaine group=76.72±6.72 mmHg, nalbuphine group=77.53±6.30 mmHg; p-value=0.579) [Table/Fig-3,4]. Similarly, a steep fall in MAP was also noted in both the groups. 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 nalbuphine group [Table/Fig-5].



[Table/Fig-3]: HR at different time intervals in bupivacaine and nalbuphine group.



[Table/Fig-4]: MAP at different time intervals in bupivacaine and nalbuphine group.

VAS at rest	Bupivacaine group Mean±SD	Nalbuphine group Mean±SD	p-value (Mann-Whitney U-test)
IAR	3.50±0.716	3.33±0. 616	0.258
1 h	2.88±0.791	2.52±0.640	**0.028**
4 h	2.12±0.686	2.03±0. 577	0.527
8 h	1.75±0 .670	1.60±0.496	0.258
12 h	1.28±0.506	1.30±0.464	0.854
16 h	1.08±0.267	1.13±0.335	0.462
24 h	1.03±0.158	1.00±0.000	0.313
VAS at movement			
IAR	4.07±0.572	3.50±0.506	**<0.0001**
1 h	3.48±0.784	3.70±0.687	0.185
4 h	2.70±0.687	2.93±0.656	0.129
8 h	2.37±0.586	2.35±0.533	0.873
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

[Table/Fig-5]: VAS score at rest and movement at different time intervals.
IAR: Immediately after recovery

The mean time of first rescue analgesic in nalbuphine group was 20.25±7.983 minutes, while in bupivacaine group it was 26.9±6.95 minutes (p-value-0.0002).

Only three patients in nalbuphine group requested for an additional analgesic (tramadol), while four in bupivacaine group did the same. In bupivacaine group, eight patients (20%) and in nalbuphine group, 10 (25%) patients developed shoulder pain during the 24 hour period.

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 [Table/Fig-6].

Variables	Bupivacaine group	Nalbuphine group	p-value
Shoulder pain	8	10	0.2425
PONV	5	14	
Itching/others	0	0	
Total	13	24	

[Table/Fig-6]: Postoperative complications.
A paired t-test for 2 independent variables; not significant

DISCUSSION

This study was conducted to determine whether bupivacaine and 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). HR and MAP of the patients of both groups were under normal ranges during the recovery period. 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 [13,14], others have shown that they are not [4,12]. The studies, which found intraperitoneal instillation of drugs effective, have been on various drugs especially local anaesthetics and opioids [15]. 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 CO_2, 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 [16].

Gupta R et al., had studied the efficacy of intraperitoneal fentanyl and bupivacaine in laparoscopic surgeries [2]. 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 nalbuphine than in patients given intraperitoneal bupivacaine. In agreement with this result, Visalyaputra S et al., [17] 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 [2,8,18].

Akinci SB et al., compared the intraperitoneal and intravenous tramadol in laparoscopic cholecystectomy for postoperative analgesic action [10]. 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 [19,20]. This was not in concurrence

with present study findings. This may be because none of these studies used intraperitoneal nalbuphine.

Limitation(s)

The non inclusion of well-defined predictors of postoperative pain like preoperative anxiety and pre-existing pain condition is a primary limitation. The second limitation is the failure to evaluate pain beyond 24 hours.

CONCLUSION(S)

This study supported the proposed hypothesis that intraperitoneal 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, though having a little more unwanted side-effects than bupivacaine.

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