RESEARCH PAPER

Comparative efficacy of Intraperitoneal Bupivacaine, Bupivacaine with Tramadol, Bupivacaine with Clonidine for postoperative analgesia in Laparoscopic Cholecystectomy: A prospective randomized control trial

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ABSTRACT

Background: Bupivacaine is a long-acting local anaesthetic and is well known for its analgesic efficacy. Intraperitoneal injections of local anaesthetics (IPLA) like bupivacaine or levobupivacaine and combination of adjuvants such as dexmedetomidine, clonidine, tramadol, ketamine and magnesium sulphate have shown promising results in managing postoperative discomfort following laparoscopic cholecystectomy. Objective of the present study was to compare the efficacy of intraperitoneal bupivacaine, bupivacaine with tramadol and bupivacaine with clonidine for postoperative analgesia in laparoscopic cholecystectomy patients.

Methods: Patients were randomized to receive one of the three study solutions: Group A received 20 ml Bupivacaine 0.25% with normal saline; Group B received 20 ml of Bupivacaine 0.25% with Tramadol (1mg/kg); and Group C received 20 ml of Bupivacaine 0.25% with Clonidine (1µg/kg), all made up to a total volume of 25 ml. after taking patient under general anaesthesia, drug solutions were instilled just prior to trocar removal. Postoperative pain was recorded using VAS score for 24 hours after surgery. Postoperative shoulder pain, nausea, vomiting and time taken for rescue analgesia was noted.

Results: A total of 120 patients were enrolled. Mean VAS scores were significantly different between the three groups at all time points (1 hr, 2 hrs, 4hrs, 6, 12 and 24 hrs). Group C consistently showed the lowest VAS pain scores throughout the 24-hour observation period. Group A had the highest requirement (33 patients, 82.5%) of rescue analgesia, followed by Group B (25 patients, 62.5%), and Group C (15 patients, 37.5%) ($p<0.0001$). There is not significant change in hemodynamic parameters and negligible side effects.

Conclusion: Intraperitoneal instillation of bupivacaine with clonidine provides superior postoperative analgesia compared to bupivacaine alone or bupivacaine with tramadol following laparoscopic cholecystectomy.

Keywords: Laparoscopic Cholecystectomy, Bupivacaine, Tramadol, Clonidine, Post operative Analgesia.

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INTRODUCTION

A National Institutes of Health consensus statement in 1992 stated that laparoscopic cholecystectomy provides a safe and effective treatment for most patients with symptomatic gallstones and has become the treatment of choice for many patients. This procedure has more or less ended attempts at non-invasive management of gallstones [1]. The initial driving force behind the rapid development of laparoscopic cholecystectomy was patient demand. Hence, laparoscopic cholecystectomy was introduced and gained acceptance not through organized and carefully conceived clinical trials but through acclamation [2,3]. Laparoscopic cholecystectomy decreases postoperative pain, decreases the need for postoperative analgesia, shortens the hospital stay from 1 week to less than 24 hours. Laparoscopic

cholecystectomy also provides improved cosmesis and improved patient satisfaction as compared with open cholecystectomy [4].

Effective analgesic treatment after laparoscopic cholecystectomy has remained a clinical challenge. Several analgesic interventions with varying targets and mechanisms have been investigated for their influence on early pain after laparoscopic cholecystectomy. Variable analgesic effects of periportal infiltration of local anaesthetics, infiltration of the periportal parietal peritoneum, intraperitoneal spraying above the gall bladder, instillation into the sub-diaphragmatic space and into the sub-hepatic space covering the area of hepatoduodenal ligament have been reported [5].

The level of pain usually peaks during the first few days after surgery and then gradually decreases over the next few days. The stretching of the intra-abdominal cavity causes pain following laparoscopic surgery and peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide (CO2) in the peritoneal cavity [6].

Intraperitoneal instillation of local anaesthetic agents alone [7] or in combination with opioids [8,9], □ 2 agonists such as clonidine [21] and dexmedetomidine [8] have been found to reduce post operative pain following laparoscopic cholecystectomy. The same acts by blocking local nerve endings and vagal signals in peritoneum. Popularly used drugs are 0.25% to 0.5% Bupivacaine, levobupivacaine and ropivacaine along with adjuvants like magnesium sulphate, ketamine, tramadol, fentanyl, dexmedetomidine and clonidine. The idea of drugs to be given intraperitoneally has significant advantages like longer duration of analgesia leading to long time for rescue analgesia and improved comfort in first few hours of surgery along with fewer side-effects associated with systemic drugs. Objective of the present study was to compare the efficacy of intraperitoneal bupivacaine, bupivacaine with tramadol, bupivacaine with clonidine for postoperative analgesia in laparoscopic cholecystectomy patients at tertiary care hospital.

MATERIAL & METHODS

This is prospective, randomized, triple blind clinical study conducted in department of anaesthesia. A total of 120 adult patients aged between 18 and 65 years, according to the American Society of Anaesthesiologists (ASA) physical status I or II, who were scheduled for elective laparoscopic cholecystectomy, were enrolled in the present study. Participants were randomly allocated into three parallel groups of 40 patients each using a computer-generated random number table to ensure unbiased assignment. Patient were excluded if they refused participation, had a known allergy to the study drugs, suffered from chronic pain conditions, were on regular analgesic medication, were pregnant, had severe cardiac, hepatic, or renal disease, or if the surgery was converted to an open cholecystectomy.

Allocation concealment was maintained using sequentially numbered, sealed, opaque envelopes which were opened only after the patient was enrolled. Operating surgeon and the anaesthesiologist were administered the drug, and the outcome assessors were blinded to the group allocation. Patients were randomized to receive one of the three study solutions: Group A received 20 ml Bupivacaine 0.25% with normal saline; Group B received 20 ml Bupivacaine 0.25% with Tramadol (1mg/kg); and Group C received 20 ml Bupivacaine 0.25% with Clonidine (1 mcg/kg), all made up to a total volume of 25mL. All patients underwent a pre-anaesthetic assessment for eligibility of patient. Baseline investigations are done. After confirming fitness of patient, they are advised fasting of 8 hours and were premedicated with tab alprazolam0.25 mg and tab ranitidine 150 mg orally at night and two hours before surgery in the morning.

After transferring patient to operating room, multipara monitors were attached for various baseline and intraoperative parameters. Intravenous cannula (18 G) was secured in all patients and crystalloids were given at 20ml kg/hr. Premedication was done with inj. Midazolam (0.05 mg/kg), inj. Glycopyrrolate (0.005mcg/kg). Preoxygenate the patient for 3-4 minutes and induction done with fentanyl (2mcg/kg) and propofol (2mg/kg). Tracheal intubation done with vecuronium (0.1mg/kg) after adequate relaxation. Maintenance was done with sevoflurane in with oxygen and muscle relaxants. Minute ventilation adjusted to maintain normocapnia (end tidal CO2 between 34 and 38mm Hg).

Laparoscopic cholecystectomy was done after positioning the patient, using three port technique and pneumoperitoneum was created using carbon dioxide, maintaining intra-abdominal pressure at 10-12 mmHg. At the end of the surgery, prior to trocar removal, the assigned study solution was instilled intraperitoneally at the gall bladder bed through the epigastric port under direct laparoscopic visualization. Patient reversed with IV neostigmine and IV glycopyrrolate for reversing neuromuscular block. The primary outcome was postoperative pain, assessed using the Visual Analog Scale (VAS) (0–10) at 1, 2, 4, 6, 12 and 24 hours postoperatively. Secondary outcomes included the time to first rescue analgesia, total rescue analgesic consumption, and hemodynamic parameters (heart rate and blood pressure) and patient satisfaction score recorded at regular intervals. Rescue analgesia (Tramadol 1 mg/kg IV) was administered if the VAS score was ≥4 or upon patient request. As we have discussed, primary objective of the study is to provide postoperative analgesia to patient

undergoing laparoscopic cholecystectomy and in process of finding a best and affordable analgesia we have taken account of clonidine, which is a highly potent alpha-adrenergic agonist and perfect alternative to dexmedetomidine. And we wanted to compare the efficacy of tramadol (opioid-sparing) with that of clonidine in terms of duration of analgesia, side effect profile and difference in VAS score as both drugs are easily and commonly available in our setups. So, this demonstrates we can give a multimodal and affordable approach of analgesia to our patients without spending much of our resources.

Visual analogue scale (VAS) 0- absolutely no pain, 1-3 mild pain, 4-6 moderate pain, 7-9 severe pain, 10 maximum intolerable pain.

Patient satisfaction score (PSS) is number of positive responses from total survey response. Likert scale uses standard 1-5 scale and only top ratings either 4 or 5 counted as satisfied.

Adverse effects such as nausea, vomiting, pruritus, bradycardia, hypotension, and sedation were monitored and recorded throughout the 24 hours observation period.

STATISTICAL ANALYSIS

Data was analysed with the help of IBM SPSS version 26 software. Mean and Standard deviations were observed. One-Way ANOVA test, Chi-Square test and post-hoc test was applied. P-value was taken less than or equal to 0.05 ($p \leq 0.05$) for significant differences.

RESULTS

A total of 120 patients were enrolled in the present study. All patients were categorized into three group (Group A, Group B and Group C). Each group had 40 patients. All three groups were compared. Gender, Age and duration of surgery of all three group patients were not significantly different ($p>0.05$). While, BMI was significantly different in all three group patients ($p=0.014$).

Table 1: Distribution of baseline variables

Baseline variables	Group A (n=40)	Group B (n=40)	Group C (n=40)	P-value
M:F	15:25	16:24	14:26	0.90
Mean age (years)	36.42±10.21	36.56±9.76	35.9±9.28	0.950
Mean BMI (kg/m2)	25.42±2.7	26.82±2.14	27.02±2.86	0.014
Duration of surgery	91.48±10.68	89.61±12.74	92.38±10.28	0.52

Mean VAS scores were significantly different between the three groups at all time points. Group C consistently showed the lowest pain scores throughout the 24-hour observation period. Group C patients showed significantly lower scores compared to both Group A and Group B ($p<0.01$) during 4 to 6 hours.

Table 2: Mean VAS scores over the 24 hours

Visual Analogue Scale	Group A	Group B	Group C	P-value
	Mean±S.D	Mean±S.D	Mean±S.D	
Base Line	1.842±0.7	1.248±0.8	1.0±0.9	P=0.0000
1 hour	6.234±2.1	4.8±1.5	3.275±0.7	P<0.0001
2 hours	5.8±2.89	4.9±1.75	4.124±0.8	P=0.006
4 hours	4.642±1.6	3.8±1.7	3.048±1.8	P=0.0002
6 hours	4.024±2.4	3.647±1.4	2.8±0.7	P=0.004
12 hours	3.894±1.4	2.9±1.3	2.2±0.9	P<0.0001
24 hours	2.843±0.6	2.142±0.7	1.362±0.4	P<0.0001

The requirement for rescue analgesia was significantly different between groups. Group A had the highest requirement (33 patients, 82.5%), of rescue analgesia followed by Group B (25 patients, 62.5%), and Group C (15 patients, 37.5%) (p<0.0001).

Table.3. Mean doses of rescue analgesia over the 24 hours

Dose of Rescue Analgesia	Group A	Group B	Group C	P-value
	Mean±S.D	Mean±S.D	Mean±S.D	
Base Line	0	0	0±0	P<0.0001
1 hour	39.8±36.92	10.7±25.75	0±0	P<0.0001
2 hours	34.64±35.65	58±32.8	63 ± 27.64	P=0.0005
4 hours	40.4±35.62	20.6±33.24	10.8±26.3	P=0.0003
6 hours	33.4±36.21	58±29.54	0±0	p<0.0001
12 hours	38±37.64	10.64±29.62	0±0	p<0.0001
24 hours	11±27.28	3.27±10.82	0±0	P=0.03

Heart rate and blood pressure remained stable throughout the observation period in all three groups. No clinically significant differences were observed between groups at any time point (p>0.05). All patients maintained hemodynamic stability without requiring any intervention.

The incidence of adverse effects was generally low across all groups. Nausea/vomiting was more common in Group B (6 patients, 15%) compared to Group A (4 patients, 10%) and Group C (3 patients, 7.5%). Pruritus was observed only in Groups A (1 patient, 2,5%) and group B (4 patients, 10%), with no cases in Group C. Bradycardia was observed only in group A (1patient, 2,5%) and group C patients (3 patients, 7.5%). Bradycardia (heart rate< 60bpm) was observed in 1 patient in group A and 4 patients in group B. But it was mild and did not require treatment.

Sedation was more common in Group C (6 patients, 15%) but was mild and did not cause any respiratory depression or other complications.

Table 4: Side effect profile

Side Effects	Nausea/Vomiting	Pruritus	Bradycardia
Group A	4(10%)	1(2.5%)	1(2.5%)
Group B	6(15%)	4(10%)	0(0.00%)
Group C	3(7.5%)	0	3(7.5%)
Total	13(10.84%)	5(4.17%)	4 (3.33%)

Patient satisfaction scores were significantly higher (p<0.0001) in Group C (10.23±2.45) compared to Group B (8.74±2.36) and Group A (7.28±2.56).

DISCUSSIONS

Laparoscopic cholecystectomy is gold standard surgical treatment for cholelithiasis and it is among the most commonly performed elective surgical procedure. Since its introduction, the minimal invasive approach has largely replaced open cholecystectomy because of its well establish advantages, including reduced post-operative pain, shorter hospital stay, faster recovery, improved cosmetic outcome and lower overall morbidity. However, despite its minimally invasive nature, patients frequently experience moderate postoperative pain, particularly during first 24 hours after surgery arising from port site incisions, visceral manipulation, diaphragmatic irritation

caused by residual carbon dioxide pneumoperitoneum [10,11,12].

Laparoscopic cholecystectomy is a part of day care surgeries nowadays. Effective pain control is cornerstone component of the same and plays a crucial role in ensuring successful patient outcome. Since patients are discharged on same day of surgery, adequate analgesia is essential to facilitate early mobilisation, improve patient comfort, reduce postoperative nausea and vomiting, minimise unplanned hospital admissions or delayed discharge.

Intraperitoneal instillation of analgesic agents has emerged as a simple, safe, and effective technique for reducing postoperative pain following laparoscopic cholecystectomy [13]. By directly acting on the peritoneal nociceptors and attenuating the inflammatory response induced by pneumoperitoneum and surgical manipulation, intraperitoneal analgesia provides effective visceral pain relief while minimising systemic adverse effects [14].

As we have three comparison groups with bupivacaine, bupivacaine with tramadol and bupivacaine with clonidine. Bupivacaine, a long-acting amide local anaesthetic, block voltage gated sodium channel, thereby preventing nerve impulse conduction. When instilled intraperitoneally, it provides prolonged visceral analgesia, decreases postoperative pain scores, reduces opioid consumption [15]. And addition of clonidine, an alpha-adrenergic agonist, enhances the analgesic efficacy of bupivacaine through both peripheral and central mechanisms. Clonidine prolongs the duration of analgesia, provide mild sedation and anxiolysis without causing significant respiratory depression [23]. Clonidine, has emerged as an economical alternative to dexmedetomidine for intraperitoneal instillation as an adjuvant to bupivacaine. Although dexmedetomidine possesses greater alpha-2 adrenergic receptor selectivity and may prolong the duration of analgesia to a greater extent, clonidine has demonstrated comparable opioid-sparing effects and satisfactory analgesia at a substantially lower cost, making it a practical option in resource-constrained settings [16]. Tramadol, a centrally acting analgesic with weak mu-opioid receptor agonist activity and inhibition of serotonin and norepinephrine reuptake [17].

Result of the present study found the intraperitoneal instillation of bupivacaine with clonidine provides superior postoperative analgesia compared to bupivacaine alone or bupivacaine with tramadol following laparoscopic cholecystectomy. the combination resulted in significantly lower pain scores, reduced rescue analgesic requirements, and prolonged time to first rescue analgesia.

Our findings are consistent with previous studies that have demonstrated the superior analgesic efficacy of bupivacaine clonidine combinations. Govil N et al reported similar findings in their study with levobupivacaine with or without clonidine in laparoscopic cholecystectomy patients. They demonstrated higher efficacy in clonidine group and reduced analgesia as well [18]. The prolonged analgesia observes in our study can be due to clonidine property to augment bupivacaine local anaesthetic effect.

A study by Topno N et al conducted in 100 patients studied analgesic effect t of intraperitoneal bupivacaine with or without tramadol. They observed that there was significant difference in postoperative pain profile in placebo group versus bupivacaine group and placebo group versus bupivacaine plus tramadol group [19]. Tramadol's dual mechanism of action, involving both opioid receptor agonism and inhibition of serotonin and norepinephrine uptake contributes to its analgesic properties.

Systemic review and meta-analysis by Kahokehr A et al described the reduction of abdominal pain, incidence of shoulder pain and postoperative opioid consumption after intraperitoneal instillation of local anaesthesia (IPLA) [20]. Hamid AM et al also concluded that patients who received intraoperative levobupivacaine instillation had profound postoperative analgesia [21].

Shukla U et al in their study done on 120 patients, where they had three groups- bupivacaine alone (B), bupivacaine with dexmedetomidine (BD) and bupivacaine with tramadol (BT). They inferenced that, definitely bupivacaine combination with dexmedetomidine is better and superior to bupivacaine alone and may be better than bupivacaine with tramadol. So, for better exploration, we have conducted this study between bupivacaine with tramadol versus bupivacaine with clonidine, a more cost friendly alternative to dexmedetomidine and our study results proved the same [22].

Memis et al. studied the effects of tramadol or clonidine added to intraperitoneal bupivacaine, on post operative pain in 60 total abdominal hysterectomy patients and found that combination of tramadol or clonidine with intraperitoneal bupivacaine to be more effective than bupivacaine alone. They found no significant difference between tramadol and clonidine groups in terms of efficacy but we found clonidine to have significantly better efficacy than tramadol in combination with bupivacaine [23].

Kaarthika T et al studied 108 patients undergoing laparoscopic cholecystectomy and compared IPLA by bupivacaine with dexmedetomidine versus bupivacaine

with clonidine. They concluded that alpha-2 agonist addition to bupivacaine intraperitoneally significantly reduces amount of opioid consumption postoperatively and dexmedetomidine group provide longer period of postoperative analgesia as compared to clonidine [16].

Singh AR et al compared instillation of bupivacaine with magnesium sulphate with bupivacaine with dexmedetomidine for postoperative analgesia after laparoscopic cholecystectomy and findings are in favour of magnesium sulphate which shows superior analgesia in comparison to dexmedetomidine. As magnesium is a cost effective, readily available adjuvant that may be considered a better alternative in multimodal analgesia (MMA) in postoperative period [24].

Patient satisfaction scores were highest in the clonidine group, reflecting the superior pain control achieved with this combination. The finding has important implications for patient-centred care and overall treatment outcomes.

The incidence of adverse effects was generally low and manageable across all groups. The hemodynamic stability observed across all groups is reassuring and consistent with the safety profile of intraperitoneal local anaesthetic instillation The higher incidence of nausea and vomiting in tramadol group is likely related to tramadol's serotonergic effects. The sedation observed in clonidine group, while more frequent than in other groups, was not associated with respiratory depression or other serious complications. The mild bradycardia observed in the clonidine group is expected due to alpha 2-adrenergic agonist properties but was clinically insignificant and did not require intervention [25].

CONCLUSIONS

The present study concluded that the combination of bupivacaine with clonidine significantly lower pain scores, reduced rescue analgesic requirements, prolonged time to first rescue analgesia, and higher patient satisfaction scores. Use of bupivacaine with clonidine is an effective, cost-effective and safe option for postoperative pain cholecystectomy. Hence, Intraperitoneal instillation of bupivacaine with clonidine provides superior postoperative analgesia compared to bupivacaine alone or bupivacaine with tramadol following laparoscopic cholecystectomy, without significant adverse effects.

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