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Original Research Article

# A PROSPECTIVE RANDOMISED CONTROLLED STUDY TO COMPARE THE POSTOPERATIVE ANALGESIC EFFECTIVENESS OF INTRAPERITONEAL INSTILLATION OF BUPIVACAINE, TRAMADOL AND COMBINATION OF BOTH IN LAP CHOLECYSTECTOMY

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## Abstract

**Background:** The study was conducted to compare the postoperative analgesic efficacy of intraperitoneal instillation of bupivacaine, tramadol and combination of both in lap cholecystectomy under General anaesthesia, to hasten recovery in day case surgery, decrease the side effects of opioid use and mitigate the post laparoscopic cholecystectomy shoulder pain and other side effects. **Materials and Methods:** Total of 80 patients were randomly distributed into four groups of twenty participants each, An informed written consent from the patients and approval from the local ethics committee was obtained. Group I 'C' received 50 ml of 0.9% saline (control), Group II 'B' Patients received 50 ml of 0.25% bupivacaine, Group III 'T' Patients received 50 ml of saline containing 100 mg of tramadol and Group IV 'TB' received 50 ml of 0.25% bupivacaine with 100 mg of tramadol. **Result:** Postoperative pain was assessed using visual analogue scale (VAS), consisting of 10 cm scale representing varying intensity of pain from 0 cm (no pain) to 10 cm (worst imaginable pain).All the four groups were comparable in age, weight, sex distribution and duration of surgery. The difference between them was statistically insignificant. Intraperitoneal instillation of tramadol provided longest duration of analgesia for 720 +/- 35.37 minutes. There was reduced incidence and severity of shoulder pain which was comparable in all the four groups with no statistical significance. No significant side-effects were seen in any of the groups. **Conclusion:** Intraperitoneal instillation of bupivacaine and tramadol used alone or in combination in reduced dosages is an effective and safe method of providing prolonged postoperative analgesia for patients undergoing laparoscopic cholecystectomy. Moreover, both the drugs serve as adjuncts to analgesics used in the postoperative period.

## INTRODUCTION

As laparoscopic surgeries are gaining popularity, different modalities of perioperative pain management are being used. Apart from the parenteral route of analgesic use, intraperitoneal instillation of local anaesthetics and opioids are gaining popularity for better pain relief.[1] The laparoscopic approach to cholecystectomy has been proven to reduce postoperative pain significantly and shorten the recovery period, therefore, reducing discharge time from 1 day to 3 days to same day discharge with an earlier return to a normal life. Nonetheless, studies have shown that the first 24 hours to 48 hours after surgery are associated with moderate abdominal and shoulder pain in 35% to 63% of patients. Early postoperative pain is the most common complaint after elective laparoscopic cholecystectomy; pain intensity peaks during the first postoperative hours and usually declines over the following 2 days to 3 days.[2] The type of pain after laparoscopic surgery differs considerably from that seen after laparotomy. Whereas laparotomy results mostly in parietal pain, patients after laparoscopic cholecystectomy complain more of visceral pain resulting from the stretching of intraabdominal cavity, peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity. Intraperitoneal (IP) administration of some drugs can be effective for pain relief after


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laparoscopic surgery.[3] The first successful laparoscopic cholecystectomy was performed by Mouret in France in 1987, but it was not until the reports by Reddick and DIsen (1989) and Dubois et al. (1990) that laparoscopic cholecystectomy became widely acceptable.[4] Postoperative pain management has acquired a central role in the ambulatory surgery in order to facilitate earlier hospital discharge.[5] Suitability of patient discharge from the inpatient facility depends upon adequacy of postoperative pain control.[6] Inadequate analgesia during the postoperative period may have various short and long term consequences.[7] Peripheral use of local anaesthetics for postoperative pain relief has become a popular practice in many open surgical procedures. The benefit of wound infiltration in open abdominal surgery appears most promising after minor procedures such as hernia repair; however, it is less beneficial in moderate to major procedures. Compared with open procedures, laparoscopic surgery being a minimally invasive technique is associated with reduced surgical trauma and accordingly is often performed as day care surgery. Peripheral use of local anaesthetics after laparoscopic surgery may, therefore, as in the case of minor open procedures, be more likely to provide clinically relevant postoperative pain relief in the early postoperative period.[8] The intraperitoneal route of administration of local anaesthetics is simple, does not involve additional central neuraxial block and is particularly suited to the practice of ambulatory anaesthesia.[9] The rationale for this route of administration is that the peritoneum is exposed to block of visceral nociceptive conduction, thereby providing an additional mechanism of analgesia.[10] Numerous clinical studies have investigated the use of regional local anesthetics, in combination with other modalities for pain relief following laparoscopic cholecystectomy to avoid the adverse effects of opioids, which may delay recovery and hospital discharge. Thirteen controlled studies have investigated the analgesic effects of bupivacaine administered in the right sub diaphragmatic or gallbladder region; only 7 of the 13 trials found that the overall pain scores were significantly reduced as compared with those of the control patients.[11] Beneficial effects of bupivacaine have been found in postoperative analgesia by instillation into the wound following herniorrhaphy.[12] Direct local wound perfusion of 0.5% bupivacaine provides satisfactory pain relief and is a safe and feasible alternative to parenteral opioids.[13] Lee et al. (2001) reported that incisional and intraperitoneal bupivacaine is effective in decreasing somatic pain during first three postoperative hours. The introduction of long acting local anaesthetic drugs such as bupivacaine hydrochloride has led to renewed interest in these agents for local infiltration of the wound.[14] It has been observed that there is reduction in postoperative shoulder pain in minor gynaecological surgery after intraperitoneal instillation of local anaesthetic.[15] Local anaesthetic effects of opioids have been demonstrated in both clinical and laboratory studies.[16] Tramadol is a weak opioid and is effective local anaesthetic in minor surgeries.[17] It has selective effect on the N receptors with local anaesthetic action on peripheral nerves.[18] Laparoscopic cholecystectomy is commonly performed procedure for treating symptomatic gallstones.

This study was designed to evaluate the effect of intraperitoneal administration of tramadol and/or bupivacaine on pain relief in patients undergoing laparoscopic cholecystectomy.

## MATERIALS AND METHODS

The present study was conducted in the Postgraduate Department of Anaesthesiology and Intensive Care of our tertiary level care hospital after obtaining ethical committee clearance. Total eighty patients of ASA-I/II category, of either sex, in the age group 20 to 60 years were enrolled for the study to undergo elective laparoscopic cholecystectomy. Before admission to the study, all the patients were informed about the aims, methods, anticipated benefits and potential hazards of the study. An informed written consent from the patients and approval from the local ethics committee was obtained.

**Following patients were excluded from the study:** Patients with previous abdominal surgery, Patients with acute cholecystitis, Patients with contraindications to tramadol or bupivacaine and Patients in whom the surgery was converted into conventional cholecystectomy by the surgeon due to any reason. Pre-anaesthetic check-up was done a day before surgery and included a detailed history and complete general physical and systemic examination. Baseline values of pulse, blood pressure and respiratory rate were recorded. Basic demographic characteristics like age, sex and weight were noted.

Routine investigations included haemoglobin, clotting time, bleeding time, skiagram chest, electrocardiogram, serum urea, serum creatinine, serum electrolytes, blood sugar, serum bilirubin, liver enzymes (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and alkaline phosphatase), prothrombin time (PT) and prothrombin time index (PTI). Patients were kept fasting overnight and were premedicated with tablet alprazolam 0.25 mg at bed time. Patients were randomly allocated into four groups of 20 each according to composition of instilled solution.

**Group I 'C':** Patients in this group received 50 ml of 0.9% saline (control). Group II 'B': Patients in this group received 50 ml of 0.25% bupivacaine. Group III 'T': Patients in this group received 50 ml of saline containing 100 mg of tramadol Group IV 'TB' :Patients in this group received 50 ml of 0.25% bupivacaine with 100 mg of tramadol. The allocation was undertaken with the help of table of random numbers. In order to keep the number equal in each group, permuted block randomization was performed. In the operation theatre, intravenous line


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was established. Patient was connected to monitors to measure heart rate (HR), non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), oxygen saturation (SPO2) and electrocardiogram (ECG). After pre-oxygenating the patient with 100% oxygen for 3 minute: induction was carried out in all patients with intravenous fentanyl 1.5ug/kg, propofol 2 mg/kg, and patient was intubated with oral cuffed endotracheal tube after giving rocuronium 1.2 mg/kg and maintenance with oxygen (02), air (50:50%) and isoflurane (MAC- 1.2%).

## RESULTS

Postoperative pain was assessed using visual analogue scale (VAS), consisting of 10 cm scale representing varying intensity of pain from 0 cm (no pain) to 10 cm (worst imaginable pain). The data was analysed with the help of computer software Microsoft Excel and SPSS for Windows. The results were reported as mean and standard deviation for quantitative variables and percentage for qualitative variables. Difference in percentages among groups was assessed using chi-square test. Statistical significance among mean differences was evaluated using one-way analysis of variance (ANOVA). A p-value of < 0.05 (two-tailed) was considered statistically significant. Analysis was done according to intention to treat principle.

**Table 1**

| Age (Years) | Group C | Group B | Group T | Group TB | Statistical Inference |
|---|---|---|---|---|---|
| Mean ±SD | 38.25 ±6.99 | 38.30 ±9.44 | 39.15± 8.88 | 38.40±7.42 | p>0.05 |
| Weight (Kg) Mean ±SD | 59.15±5.26 | 58.70±4.80 | 60.10±5.30 | 60-20±6.02 | p>0.05 |

**Table 2: Demographic Parameters**

| Sex | Group C | Group B | Group T | Group TB | Statistical Inference |
|---|---|---|---|---|---|
| Male | 17 | 17 | 16 | 15 | p>0.05 |
| Female | 3 | 3 | 4 | 5 | |

**Table 3: Total duration of surgery and time duration of first analgesic rescue dose used**

| Surgical Duration in minutes (Mean ±SD) | Group C | Group B | Group T | Group TB | Statistical Inference |
|---|---|---|---|---|---|
| | **50.15±8.20** | **51.50 ±7.08** | **50.50±7.41** | **51.25±7.75** | **p>0.05** |
| 1st Dose of rescue Analgesia (Time in minutes) (Mean ±SD) | 34.75±14.37 | 541.5±131.48 | 720±35.37 | 610±65.64 | P=0.000 (Significant) |

**Figure 4: total number of patients with shoulder pain**

| Variable | Group C | Group B | Group T | Group TB | Statistical Inference |
|---|---|---|---|---|---|
| NO of patients with Shoulder pain n(%) | 5(25) | 4 (20) | 2 (10) | 3(15) | p>0.05 |

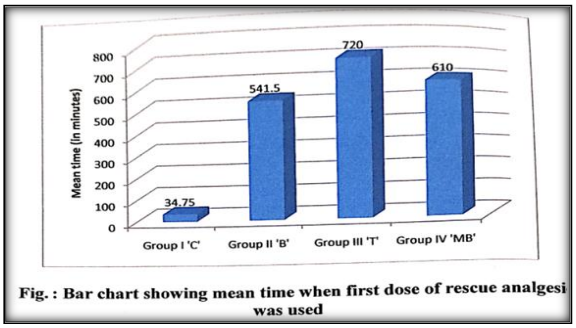

Fig. : Bar chart showing mean time when first dose of rescue analgesi was used

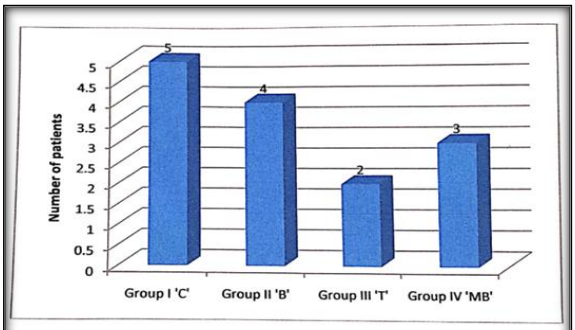

Fig.: Bar chart showing incidence of shoulder pain


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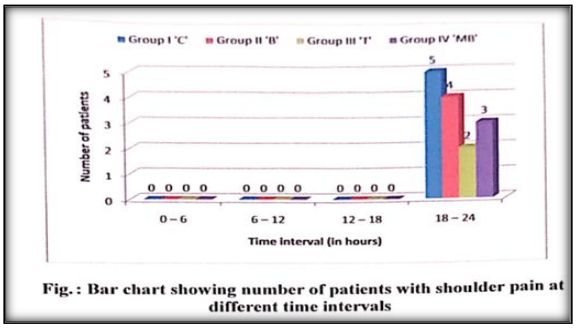


**Fig. : Bar chart showing number of patients with shoulder pain at different time intervals**

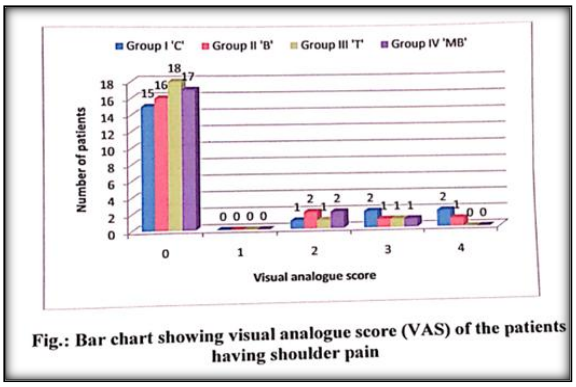


**Fig.: Bar chart showing visual analogue score (VAS) of the patients having shoulder pain**

## DISCUSSION

Postoperative pain is an inevitable consequence of any surgery. This issue has been the centre of attention of all clinicians and the modern day research has been continuing in achieving a pain free postoperative period. Given the increasing trend of day care surgery and early hospital discharge vis-à-vis the financial burdens over the patients/institutions, role of pain relief via local wound infiltration is increasingly getting common. As part of research for postoperative pain control, instillation of surgical wounds with local anaesthetic has now been found to be effective in many studies (Altunkaya et al., 2004; Demiraran et al., 2006; Kargi et al., 2010). Tramadol has local anaesthetic effects with minimal sedation and no cardiovascular compromise (Gercek et al., 2004; Guven et al., 2005). In our study, patients were randomly divided into four groups: Group I 'C' (control), Group II 'B', Group III T' and Group IV 'TB' of 20 patients each. Patients in Group I 'C' received 50 ml of 0.9% saline. Group II 'B' patients received 50 ml of 0.25% bupivacaine. Group III 'T patients received 50 ml of saline containing 100 mg of tramadol and Group IV 'TB patients received 0.125% bupivacaine with 100 mg of tramadol to a total volume of 50 ml. All the four groups were comparable in age, weight, sex and duration of surgery and the difference between them was statistically non-significant. Because the measurement of postoperative pain level is rather subjective with the use of visual analogue scale (VAS) (spontaneous pain estimation), determination of analgesic requirement in 24 hours was also done to strengthen the results. Mean time when first dose of rescue analgesic (diclofenac sodium) was used in Group I 'C' was 34.75 # 14.37 minutes, in Group II 'B' was 541.5 + 131.48 minutes, in Group III 'T was 720 35.37 minutes and in Group IV 'TB' was 610 +65.64 minutes. Statistically, the difference was found to be highly significant (p=0.000). In the present study, dose of 125 mg of bupivacaine (i.e. 50 ml of 0.25%) was used. The results are comparable to those of Bhardwaj et al. (2002) who utilized 100 mg (i.e. 20 ml of 0.5% bupivacaine with 1:200000 adrenaline) and reported a pain relief up to 8 hours postoperatively. The findings of the present study are also in accordance with those of Malhotra et al. (2007) who found that instillation of 100 mg bupivacaine intraperitoneally at the end of procedure resulted in pain relief of up to 8hours

The incidence and severity of shoulder pain was comparable in all the four groups and the difference was statistically non-significant. The overall incidence of shoulder pain in the present study was 17.5%. Collins et al. (1984) and Edwards et al. (1991) reported 35 to 60% incidence of shoulder pain. The reduced incidence and severity of the shoulder pain in present study could be due to careful emptying of pneumoperitoneum (Joris et al., 1995). Moreover, in all the patients in the present study, saline irrigation and suctioning was done at the end of procedure before the instillation of the prepared drugs. The reduced incidence and severity of shoulder pain could also be attributed to the instillation of the prepared solution in head down position (Boddy et al., 2006) and under both the hemidiaphragms (Cunniffe et al., 1998). Other factors like low pressure insufflation (Sarli et al., 2000), slow rate of insufflation (Berberoglu et al., 1998), and use of preemptive anti-inflammatory medication (Phinchantra et al., 2004) i.e. intramuscular diclofenac sodium in the present study could also have contributed to the lower incidence and severity of shoulder pain. Incidence of nausea and vomiting was 20% in Group I 'C' (control , 10% each in Group II 'B', Group III 'T' and Group IV TB. This was comparable in all the groups, the difference being statistically insignificant (p>0.05). This could be attributed to the prophylactic administration of ondansetron and metoclopramide to all the patients in the present study (Domino et al., 1999; Wilson et al., 2001). Subcutaneous tramadol infiltration can provide effective analgesia and anti inflammatory effects (Gercek et al., 2004). Tramadol has been shown to have potent local anaesthetic effects (Acalovschi et al., 2001; Robaux et al., 2004). Tramadol exerts its sensory blocking action by a mechanism similar to that of local anaesthetics in the form of blocking the voltage dependent sodium channels (Jou et al., 2003). Moreover calcium concentration in the test solution enhances the conduction blocking activity of tramadol and reduces it in the presence of lidocaine (Mert et al., 2002). Tramadol applied to rat sciatic nerve blocks the Na+ channel in a manner similar to lidocaine sodium channels (Jou et al., 2003) and blocks potassium channels more than lidocaine (Guven et al., 2005). The depolarization time of the compound action


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potential (CAP) is extended equally by applying both lidocaine and tramadol, while tramadol extends half the width of the CAP more than lidocaine due to its K channel blocking activity (Guven et al., 2005). The elimination pharmacokinetics of tramadol are appropriately described by a two compartment model, with a reported elimination half life of 5.1+/-0.8 hours (Shipton, 2000), while parenteral tramadol administered at the time of wound closure relieved postoperative pain for the limited time of 60-90 minutes (Coetzee and Van Loggerenberg, 1998; Akinci et al., 2008), locally infiltrated tramadol achieved a longer analgesic time than the reported elimination half life of parenteral tramadol, which might be related to its local effect rather than to systemic absorption (Nossaman et al., 2010). As in the study by Demiraran et al. (2006), there was no significant difference between the study groups in nausea and vomiting, which might be related to the dose, the route of administration, the timing of infiltration or the small sample size.

The purpose of the present study was to assess the postoperative pain after administration of bupivacaine, tramadol and combination of both the drugs in reduced dosages and to assess their efficacy as adjuncts to postoperative analgesics after laparoscopic cholecystectomy. Postoperatively, patients were observed for a period of 24 hours. Pain was assessed using visual analogue scale (VAS). Mean time when first dose of rescue analgesic (diclofenac sodium) was used was noted. The incidence and severity of postoperative shoulder and arm pain for 24 hours was charted down and presence of any complications.

The results thus obtained are summarized below: All the four groups were comparable in age, weight, sex distribution and duration of surgery. The difference between them was statistically insignificant. Intraperitoneal instillation of tramadol provided longest duration of analgesia for 720 ÷ 35.37 minutes. There was reduced incidence and severity of shoulder pain which was comparable in all the four groups with no statistical significance. No significant side-effects were seen in any of the groups.

## CONCLUSION

Intraperitoneal instillation of bupivacaine and tramadol used alone or in combination in reduced dosages is an effective and safe method of providing prolonged postoperative analgesia for patients undergoing laparoscopic cholecystectomy. Moreover, both the drugs serve as adjuncts to analgesics used in the postoperative period.

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