Intraperitoneal pre-insufflation of 0.125% bupivacaine with tramadol for postoperative pain relief following laparoscopic cholecystectomy

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Abstract

**Background and Aims:** Laparoscopic cholecystectomy is associated with a fairly high incidence of postoperative discomfort which is more of visceral origin than somatic. Studies have concluded that the instillation of local anesthetic with opioid around gall bladder bed provides more effective analgesia than either local anesthetic or opioid alone.

**Material and Methods:** The study included 90 American Society of Anesthesiologists I-II patients of age 16-65 years scheduled for laparoscopic cholecystectomy under general anesthesia. The patients received the study drugs at the initiation of insufflation of CO₂ in the intraperitoneal space by the operating surgeon under laparoscopic camera guidance over the gallbladder bed. Patients in Group T received tramadol 2 mg/kg in 30 ml normal saline, in Group B received bupivacaine 30 ml of 0.125% and in Group BT received tramadol 2 mg/kg in 30 ml of 0.125% bupivacaine intraperitoneally. Postoperative pain assessment was done at different time intervals in the first 24 h using Visual Analog Scale of 0-10 (0 = No pain, 10 = Worst pain imagined). Time to first dose of rescue analgesic and total analgesics required in the first 24 h postoperatively were also recorded. The incidence of side effects during the postoperative period was recorded.

**Results:** Reduction in postoperative pain was elicited, at 4 and 8 h postoperatively when Group BT (bupivacaine-tramadol group) was compared with Group T (tramadol group) or Group B (bupivacaine group) (P < 0.01). There was a significantly lower requirement of analgesics during first 24 h postoperatively in Group BT compared to Group B or T but no significant difference in the intake of analgesics was noted between Groups B Group T. Time to first dose of rescue analgesic was also significantly prolonged in Group BT compared to Group B or T. The incidence of nausea and vomiting was comparable in all the study groups.

**Conclusions:** Intraperitoneal application of bupivacaine with tramadol was a more effective method for postoperative pain control after laparoscopic cholecystectomy compared to intraperitoneal bupivacaine or tramadol alone.

**Key words:** Analgesia, bupivacaine, intraperitoneal, laparoscopic cholecystectomy, tramadol

Introduction

Various techniques have been used to control pain after laparoscopic cholecystectomy like intraperitoneal use of local anesthetics, tenoxicam, clonidine, nonsteroidal anti-inflammatory drugs, tramadol, morphine, β-adrenergic blockers, fentanyl but only a few have shown promising results. Multimodal approach is being currently advocated to control postoperative pain after laparoscopic cholecystectomy. An increasing number of controlled clinical trials have demonstrated the potential of peripheral opioid receptors in providing analgesia in the early postoperative period. Tramadol, an atypical opioid analgesic, has been recently advocated to have local anesthetic action besides its central action on mu opioid receptors along with noradrenergic and serotonergic effects. The effect of tramadol on peripheral nerves was confirmed by the inhibition of glutamate-induced nociceptive behavior in mice. However, studies on the peripheral effect of tramadol by intraperitoneal route have
shown inconsistent results. In a recent study by Memis et al., the combination of intraperitoneal bupivacaine plus tramadol was found to provide more effective analgesia than intraperitoneal bupivacaine alone after total abdominal hysterectomy.

The present study was designed to compare the analgesic efficacy of intraperitoneal bupivacaine 0.125% and tramadol (2 mg/kg) combination, with either intraperitoneal bupivacaine 0.125% or tramadol (2 mg/kg) after elective laparoscopic cholecystectomy.

**Material and Methods**

After approval by the Institutional Ethics Committee a prospective, randomized, double-blind study was conducted on 90 patients of American Society of Anesthesiologists I and II, aged 16-65 years scheduled to undergo laparoscopic cholecystectomy under general anesthesia. A written informed consent was obtained from all the patients. Patients with a history of psychiatric illness, alcohol or drug abuse, chronic analgesic use, history of pulmonary, renal, cardiac or any other systemic disease were excluded from the study. Randomization was done using computer generated random number table of 90 patients who were allocated to three groups of 30 patients each. Baseline parameters were noted in the preoperative room. After reassurance to allay anxiety, all patients were premedicated with intravenous (i.v) fentanyl 2 mcg/kg, dexamethasone 0.15 mg/kg and midazolam 0.03 mg/kg.

Anesthesia was induced with propofol 2 mg/kg i.v and neuromuscular blockade achieved with vecuronium bromide 0.1 mg/kg i.v. Orotracheal intubation was done with cuffed endotracheal tube, and general anesthesia was maintained with nitrous oxide:oxygen (60:40) and propofol infusion titrated to keep heart rate and blood pressure ±20% of baseline. End-tidal CO₂ was maintained between 35 and 45 mm Hg.

The patients received the study drugs at the initiation of insufflation of CO₂ in the peritoneal cavity by the operating surgeon under the visual guidance of laparoscopic camera over the gallbladder bed. Patients in Group T received intraperitoneal tramadol 2 mg/kg in 30 ml normal saline, in Group B received intraperitoneal bupivacaine 30 ml of 0.125% and in Group BT received intraperitoneal tramadol 2 mg/kg in 30 ml of 0.125% bupivacaine. The study drugs were instilled around gall bladder bed under the visual guidance of laparoscopic camera.

At the end of surgery, abdomen was completely deflated, and residual neuromuscular blockade was reversed with i.v. neostigmine 0.04 mg/kg and glycopyrrolate 0.01 mg/kg. Postoperative pain assessment was done using Visual Analog Scale (VAS) of 0-10 (0 = No pain, 10 = Worst imagined pain) by the anesthesiologist not involved in the preparation and infiltration of study drugs. First reading was recorded in the recovery room when the patient was oriented to time, place, and person (by asking name, place or date of birth) and was assigned as VAS at recovery. The pain assessment was then repeated after 4 h, 8 h and 24 h postoperatively with the patient at rest in the ward. All patients received diclofenac sodium (Novartis®) 1.5 mg/kg i.v. over 20 min as rescue analgesic on demand at a minimum interval of 6 h when VAS was >3. Breakthrough pain was controlled with i.v. pentazocine 0.3 mg/kg in increments up to a maximum dose of 0.6 mg/kg.

Time to first dose of rescue analgesic and total analgesic medication required during first 24 h were recorded. The patients were observed for side effects such as nausea, vomiting, pruritus, sedation, bradycardia, hypotension, and shivering during the follow-up period. The quality of analgesia after 24 h was assessed with the help of global pain score as excellent (>75% pain relief), good (50-74% pain relief), fair (25-49% pain relief), and poor (<25% pain relief).

All data were expressed as mean ± standard deviation, number or percentage, and analyzed and tabulated using SPSS 17.0 version. P < 0.05 was taken as significant. We have conducted a pilot study with 10 patients in each group keeping the primary target of VAS ≤3 at 4 h. A sample size of minimum 24 patients was necessary for α = 0.05 and power of study 80%. We included 30 patients in each group to further improve our results and compensate for subject loss during the study. All the patients of pilot study were later included into the main study. One-way ANOVA test and Chi-square test were used to assess differences in the demographic profile. One-way ANOVA test was applied to calculate differences in pain scores between the study groups. Chi-square test was used to assess the incidence of side effects.

**Results**

There were no significant differences between study groups according to age, body weight, and duration of operation [Table 1]. However, there were significantly more females than males in all the study groups.

Visual Analog Scale scores were significantly lower in Group BT compared to Group B or T at recovery, at 4 h and 8 h,
but there was no significant difference at 24 h [Figure 1].
There was a significantly lower requirement of analgesics
during first 24 h postoperatively in Group BT compared
to Group B or T [Table 2]. Time to first dose of analgesic
was also significantly prolonged in Group BT compared to
Group B or T.

There was a lower incidence of nausea and vomiting in Group
BT compared to other groups, but it was not statistically
significant [Table 3]. Global pain score (excellent plus good
vs. fair plus poor) was found significantly better in Group BT
compared to Group B or T [Table 4].

**Discussion**

Golubovic et al.\[13\] assessed the effects of intraperitoneal
administration of bupivacaine with intraperitoneal bupivacaine
and tramadol on pain relief after laparoscopic cholecystectomy.
They found a similar decrease in pain scores in both the
study groups. However they used higher volume (50ml of
0.25%) and concentration of bupivacaine as compared to
(30 ml of 0.125%) in our study. The higher concentration of
bupivacaine probably caused more intense analgesia resulting
in similar pain relief in both the study groups. Moreover, in
their study, the drugs were instilled in the peritoneal cavity
just before the end of surgery while in our study the drugs
were injected in the peritoneal cavity at the time of creation of
pneumo-peritoneum. Some authors\[15,16\] have suggested that
the peritoneal instillation of local anesthetics or opioids before
the nociceptive stimuli effectively suppresses the central neural
sensitization and provides a greater reduction of postoperative
pain.

Memis et al.\[14\] evaluated the effects of intraperitoneal
bupivacaine with bupivacaine plus clonidine on postoperative pain
following total abdominal hysterectomy. They found better
postoperative pain control in patients who received
intraperitoneal bupivacaine plus tramadol or intraperitoneal
bupivacaine plus clonidine compared to patients who received
intraperitoneal bupivacaine alone. In our study, a
combination of intraperitoneal bupivacaine and tramadol,
showed significantly better results than either of the two
drugs individually. This emphasizes the local analgesic
effect of tramadol on peripheral nociceptors in addition to
its effect from systemic uptake.

One of the important concerns of intraperitoneal use of
bupivacaine is the rise in the plasma concentration of the
drug due to systemic absorption from the peritoneal cavity.
Raetzell et al.\[17\] reported a rise of plasma concentration of
bupivacaine exceeding the threshold value of 2 mg/L after
intraperitoneal administration of 50 ml of 0.25% bupivacaine
during laparoscopic cholecystectomy. There was a significant
deterioration in respiratory function and increased episodes of
hypoxemia (SpO\(_2\) <92%) in the postoperative period
in these patients. Although we did not measure the plasma
concentration of bupivacaine in our study, none of the patients
in our study had any episode of hypoxemia or clinical signs of
neuro or cardiotoxicity in the postoperative period,
probably because of use of much lower dose of intraperitoneal
bupivacaine.

We, therefore, conclude that intraoperative intraperitoneal
administration of bupivacaine (0.125%) with tramadol is
an effective and apparently safe method of postoperative

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**Table 1: Demographic profile of the patients**

| Parameters          | Group B | Group T | Group BT | P            |
|---------------------|---------|---------|----------|--------------|
| Age (years)         | 25.8±13 | 32.1±10 | 28.1±7   | 0.13         |
| Sex (male/female)   | 6/24    | 5/25    | 4/26     | 0.91         |
| Weight (kg)         | 51.6±10 | 52.5±10 | 54.8±8   | 0.21         |
| Duration of surgery (min) | 48.5±7  | 45.7±7  | 45.5±7   | 0.41         |

All values are in mean ± SD except sex (male/female) which is in ratio, SD = Standard deviation

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**Table 2: Analgesic characteristics of the study groups**

| Variables                          | Group BT | Group T | Group B | P*          |
|------------------------------------|----------|---------|---------|-------------|
| Time to first dose of analgesic (h) | 4.1±1.8  | 2.0±1.5 | 1.7±1.2 | <0.001      |
| Requirement of analgesics (diclofenac) in first 24 h (mg) | 112.5±51.2 | 162.5±52.4 | 177.5±46.1 | <0.001 |
| Requirement of rescue analgesic (pentazocine) in first 24 h (mg) | 5.5±8.3 | 8.5±8.5 | 9.5±9.2 | <0.001 |

*Significance of Group BT over Group B and Group T, all values are in mean ± SD, SD = Standard deviation
The postoperative analgesic efficacy of intraperitoneal bupivacaine with tramadol for pain after laparoscopic cholecystectomy. Establishment of the safety profile, however, needs further studies.

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Table 3: Incidence of side effects in the study groups

| Side Effects | Group B (n = 30) (%) | Group T (n = 30) (%) | Group BT (n = 30) (%) | P |
|--------------|---------------------|---------------------|----------------------|---|
| Nausea       | 5 (17)              | 4 (13)              | 2 (7)                | 0.48 |
| Vomiting     | 3 (10)              | 3 (10)              | 1 (3)                | 0.54 |
| Shivering    | 3 (10)              | 5 (17)              | 5 (17)               | 0.69 |

All values are expressed as numbers and percentages (within brackets).

Table 4: Global pain scores of the study groups

| Degree | Group B (n = 30) (%) | Group T (n = 30) (%) | Group BT (n = 30) (%) | P* |
|--------|---------------------|---------------------|----------------------|----|
| Poor   | 7 (23)              | 6 (20)              | 1 (3)                | <0.001 |
| Fair   | 11 (37)             | 10 (33)             | 3 (10)               |    |
| Good   | 9 (30)              | 9 (30)              | 5 (17)               |    |
| Excellent | 3 (10)               | 5 (17)              | 21 (70)              |    |

All values are expressed as numbers and percentages (within brackets).

*Significance of global pain score (excellent + good versus fair + poor) of Group BT versus Group B or Group T.