A comparative evaluation of pre-emptive versus post-surgery intraperitoneal local anaesthetic instillation for postoperative pain relief after laparoscopic cholecystectomy: A prospective, randomised, double blind and placebo controlled study

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ABSTRACT

Background and Aims: Intraperitoneal local anaesthetic instillation (IPLAI) reduces postoperative pain and analgesic consumption effectively but the timing of instillation remains debatable. This study aims at comparing pre-emptive versus post-surgery IPLA in controlling postoperative pain after elective laparoscopic cholecystectomy. Methods: Ninety patients belonging to American Society of Anesthesiologists physical status I or II were randomly assigned to receive IPLAI of either 30 ml of normal saline (C) or 30 ml of 0.5% bupivacaine at the beginning (PE) or at the end of the surgery (PS) using a double-dummy technique. The primary outcome was the intensity of postoperative pain by visual analogue scale score (VAS) at 30 minute, 1, 2, 4, 6, 24 hours after surgery and time to the first request for analgesia. The secondary outcomes were analgesic request rate in 24 hours; duration of hospital stay and time to return to normal activity. Data were compared using analysis of variance, Kruskal-Wallis or Chi-square test. Results: For all predefined time points, VAS in group PE was significantly lower than that in groups C (P < 0.05). The time to first analgesic request was shortest in group C (238.0 ± 103.2 minutes) compared to intervention group (PE, 409.2 ± 115.5 minutes; PS, 337.5 ± 97.5 minutes; P < 0.001). Time to attain discharge criteria was not statistically different among groups. Conclusion: Pre-emptive intraperitoneal local anaesthetic instillation resulted in better postoperative pain control along with reduced incidence of shoulder pain and early resumption of normal activity in comparison to post surgery IPLAI and control.

Key words: Analgesia, bupivacaine, cholecystectomy, intraperitoneal, laparoscopy

INTRODUCTION

The origin of pain after laparoscopic cholecystectomy is multifactorial - pain arising from incision sites i.e., somatic pain, pain from gall bladder bed i.e., visceral pain and referred pain to shoulder. The most explainable cause for visceral and shoulder pain is peritoneal distension and visceral irritation caused by the creation of capnoperitoneum and surgical handling. Intraperitoneal administration of local anaesthetic agents alone or in combination with...
opioids has been found to reduce the postoperative pain and analgesic consumption effectively following laparoscopic cholecystectomy. However, the timing remains debatable. Recent advances suggest that an afferent block (with local anaesthetics) achieved before nociceptive input can reduce or eliminate the onset of central neural hyper excitability and can thus significantly reduce both intensity and duration of pain, while also delaying its onset. We hypothesised that local anaesthetic instillation into the peritoneal cavity immediately after capnoperitoneum (equivalent to pre-emptive analgesia) would be more efficient than at the end of the surgery (equivalent to post nociceptive analgesia) in controlling postoperative pain and discomfort and thus lead to an earlier discharge from the hospital.

**METHODS**

This prospective randomised double blind, double dummy trial was conducted after obtaining approval from Institutional Ethics committee and written informed consent from the study participants.

The study population comprised of 90 patients belonging to American Society of Anesthesiologists physical status (ASA PS) I and II in the age group of 18–60 years of either sex posted for elective laparoscopic cholecystectomy under general anaesthesia. Patients not willing to participate in the study, pregnant or lactating mothers, allergic to study drugs, presented with acute cholecystitis, severe cardiac, pulmonary and renal diseases were excluded from the study. Any patients who needed conversion to open cholecystectomy or insertion of a drain at the end of the procedure were also excluded from the study.

Ninety patients were randomised into three groups using computer generated random number table and sealed opaque envelope technique. Each patient received intraperitoneal instillation of either 30 ml of placebo or 0.5% bupivacaine at different timing as per their group allocation using double dummy technique.

Patients in control group (C) received 30 ml normal saline at beginning of surgery (after creation of capnoperitoneum) and at the end of the surgery (after removal of gall bladder). Patients from pre-emptive group (PE) received 30 ml 0.5% bupivacaine at the beginning of surgery and 30 ml of saline at the end of the surgery and patients from post-surgery group (PS) received 30 ml of saline at the beginning of surgery and 30 ml of 0.5% bupivacaine at the end of the surgery. Blinding was ensured by preparing the study drugs in a ready to inject coded 50 ml syringe by a trainee anaesthesia resident not involved with the study protocol. The postoperative follow-up of the study participant was done by one of the co-author blinded to the study drug administration and not involved with intraoperative management of the case.

Preoperatively, all the patients were explained about the study protocol and how to use visual analogue scale (VAS) to indicate their pain perception by identifying zero as no pain and 10 as worst imaginable pain. On arrival to the operating room a peripheral 18 G intravenous cannula under local anaesthesia was secured and standard monitoring like three lead electrocardiography, non-invasive blood pressure, oxygen saturation and end tidal CO₂ were connected and base line vital parameters noted. A standard general endotracheal anaesthesia protocol comprising of intravenous (IV) fentanyl (2 μg/kg), midazolam (0.04 mg/kg), thiopentone sodium titrated to sleep dose (4-7 mg/kg) for anaesthesia induction and vecuronium bromide (0.1 mg/kg) IV to facilitate orotracheal intubation was followed in all patients. All patients were given 0.1 mg/kg of morphine IV after induction of anaesthesia but before incision for trocar placement. Anaesthesia was maintained with 1–3% sevoflurane and 40% oxygen in air. Intermittent positive-pressure ventilation was used to adjust minute ventilation for the desired normocapnia (end tidal carbon dioxide between 34 and 38 mm Hg). During laparoscopy, intra-abdominal pressure was limited to 12–14 mm Hg. At the end of surgery, residual neuromuscular blockade was reversed with intravenous neostigmine and glycopyrrolate. The study drugs as per group allocation were instilled in equal amounts into the hepatodiaphragmatic space, near and above the hepatoduodenal ligament and above the gall bladder bed under direct vision in Trendelenburg's position. All patients were operated by the same surgical team with standard number of port placement and surgical steps. All patients received 4 mg dexamethasone IV after anaesthesia induction and 8 mg ondansetron after deflation of capnoperitoneum as prophylaxis for post-operative nausea and vomiting.

The intensity of pain was recorded for all patients using visual analogue scale at 0.5, 1, 2, 4, 6, 24 hours.
after surgery. Analgesia requirements were recorded for 24 h. If VAS score >3, patients were prescribed paracetamol 1 g IV followed by additional doses if requested by patient after an interval of 6 h and pain between 2 doses of paracetamol was treated with fentanyl 1 µg/kg IV (rescue analgesic). Time to satisfy criteria for hospital discharge was assessed by modified post anaesthesia discharge scoring system (PADSS) criteria[6] at 8.00 h and 18.00 h every day until they achieved a score of at least 9 out of 10.

The primary outcome measure of the trial was total postoperative pain severity and time to the first analgesic request in recovery room (considering time at extubation to be zero).

The secondary outcomes were analgesic request rate (number of doses of paracetamol in 24 hours); number of patient using rescue fentanyl in 24 hours; duration of hospital stay (PADSS of 9/10), incidence of shoulder pain and return to normal activity (obtained by telephonic interview).

Sample size was estimated from our pilot study which yielded a mean pain score of 4.6 with standard deviation 2.7 at second hour after surgery measured with a visual analogue scale in 10 patients who received normal saline. In order to demonstrate a 25 mm difference in VAS score 2 h after surgery among the groups for an alpha-error of 0.05 and beta-error of 0.10, we needed 25 patients per group. Assuming a dropout rate of 15%, 90 patients were required for this study.

The data obtained were evaluated for normality using the Shapiro–Wilk test. Normally distributed data were presented as mean (SD). Comparison of three groups for continuous variables were done by using analysis of variance followed by a post hoc Tukey test to find out the significance between pairs. Non-normally distributed continuous variables were expressed as a median value (inter quartile range 25–75) and was analysed using Kruskal–Wallis test with Bonferroni’s correction. Descriptive variables were presented as frequency of occurrence, percentage or number and compared using Chi-square test or Fisher’s exact test, as appropriate; P values <0.05 was considered statistically significant. All the data were checked twice. All statistical analysis were done using SPSS version 19 [IBM Inc. Chicago IL, USA, 2010].

RESULTS

In total 134 patients were screened for the study and 90 patients meeting the inclusion and not having any exclusion criteria were randomised into three groups. There were six dropouts after randomisation, two from each group as they needed drain insertion at the end of surgery for suspected bile spillage [Figure 1]. There were no significant differences among the three treatment groups in terms of patient demographics and risk stratification except that patients from control group underwent longer duration of surgery [Table 1].

None of the patients complained pain in the first 30 minutes after surgery and there after a significant difference in pain perception was found among groups.

All patients from control group had a higher pain score compared to intervention group (PE and PS) from 1st hour onward till the completion of the study period for all predefined time points.

In our study, PE group achieved a statistically significant lower VAS score for all time points over control whereas for PS group it reached statistical significance only at 4th and 24th hour [Table 2]. The time to first analgesic request was shortest in group C (238.0 ± 103.2 minutes) compared to intervention group (PE, 409.2 ± 115.5 minutes; PS, 337.5 ± 97.5 minutes; P < 0.001). However, the PE group fairs better than PS group in delaying the time to first analgesic request by about 20% over the post-surgery group (P = 0.039 by post-hoc test) [Table 2]. A statistically significant, reduction of incidence of shoulder tip pain was found at 24 hour

![Table 1: Patients’ baseline and intraoperative characteristics](image)

| Variable                  | Control (C) n=30 | Pre-emptive (PE) n=30 | Post-surgery (PS) n=30 | P    |
|---------------------------|------------------|-----------------------|------------------------|------|
| Age (yrs.)                | 41.0 (9.0)       | 46.7 (8.7)            | 41.6 (12.7)            | 0.080|
| Sex (Male/Female) (n)     | 13/15            | 11/17                 | 9/19                   | 0.540|
| Weight (kgs)              | 61 (11)          | 63.2 (10.7)           | 60.17 (8.8)            | 0.520|
| BMI (kg/m²)               | 24.2 (3.2)       | 25.0 (4.0)            | 24.2 (3.2)             | 0.660|
| ASA PS III (n)            | 23/5             | 18/10                 | 21/7                   | 0.310|
| Duration of surgery (min) | 106.8 (18.8)     | 87.1 (22.9)           | 92.6 (26.7)            | 0.007|

Data presented as mean (SD); n – Number of patients; BMI – Body mass index; ASAPS – American Society of Anesthesiologists Physical Status.
post operatively in intervention groups compared to group C ($P < 0.001$). Maximum number of patients (18 out of 28, 64%) from control group experienced shoulder tip pain in the postoperative period in contrast to only 7% (2 out of 28) from PE and 21% (6 out of 28) from PS [Table 3].

The control group needed a significantly more number of paracetamol in contrast to patients from intervention group (PE and PS). Comparison among the groups revealed that, pre-emptive group consumed least number of doses of paracetamol (2.2 ± 0.8) versus PS group (PS, 2.8 ± 0.7; $P = 0.007$) and control group (C, 3.7 ± 0.5; $P < 0.001$) [Table 3]. The number of patient requiring rescue fentanyl was significantly higher in the control group compared to intervention groups (PE and PS). Sixteen patients from control group, two patients from pre-emptive group and seven patients from post-surgery group required rescue fentanyl for pain relief ($P < 0.001$) [Table 3].

The time to achieve a score of ≥9 in PADSS was comparable among the three groups. However, the patients from control group took longer time to resume their normal activity after discharge in comparison to other two pre-emptive and post-surgery group (C, 6.2 ± 0.8 days; PE, 4.7 ± 0.6 days; PS, 5.5 ± 0.6 days; $P < 0.001$). Further post hoc analysis revealed that
pre-emptive group patients returned to their normal activity significantly much earlier compared to post surgery (PE, 4.7 ± 0.6 day; PS, 5.5 ± 0.6 day; \( P = 0.001 \)) and control group (PE, 4.7 ± 0.6 days C, 6.2 ± 0.8 days; \( P < 0.001 \)). A similar trend was also observed between post-surgery versus control group (PS, 5.5 ± 0.6 days; C, 6.2 ± 0.8 days \( P = 0.003 \)) [Table 3].

**DISCUSSION**

Even today the postoperative pain after laparoscopic cholecystectomy remains one of the major concerns while considering early discharge of patients from hospital and resumption of daily normal activity after discharge.

The primary findings of the studies are Intraperitoneal local anaesthetic instillation (IPLAI) of bupivacaine after creation of capnoperitoneum not only reduce the postoperative pain intensity in the first 24 h effectively but also result in early return to normal routine activity and reduce incidence of shoulder tip pain significantly. However, intraperitoneal infiltration of bupivacaine does not lead to early discharge from the hospital.

Two successive Cochrane review published in the same year opined that IPLAI reduces the intensity of pain perception in ASA PS I or II patients undergoing elective laparoscopic cholecystectomy.\[^{2,7}\] The second Cochrane review\[^{3}\] did not find enough evidence to determine conclusively the effects of timing of IPLAI or different drugs on postoperative pain. However, both the review suggested that, there is a need to link the clinical relevance of this reduction in pain with IPLAI to clinical outcomes in terms of attaining early discharge criteria and time to return to routine activity. Few recent studies also not analysed the effects of improved pain relief on attaining early discharge criteria or resumption of daily routine activity.\[^{8-10}\]

Our study was designed to overcome few of the shortcoming of the trials included in the previous systemic meta-analysis. We have prospectively studied not only the effects of timings of IPLAI on pain score but also the effect of improved pain relief on the clinical outcome in terms of attaining early discharge criteria and time to resume normal activity. In our study, pre-emptive group achieved a statistically significant lower VAS score at all-time points over control whereas for PS group it reached statistical significance only at 4\(^{th}\) and 24\(^{th}\) hour. Nevertheless, the VAS always remained numerically lower in PS group compared to control group. However, we did not find any significant difference in VAS score between PE versus PS group at any time points. This improved quality of analgesia resulted in prolongation of time to first analgesic request in the pre-emptive group by 70% over control group and 20% over PS group [Table 2]. As a consequence of this improved duration of analgesia PE group not only consumed less paracetamol but also less rescue analgesics compared to group C and group PS.

A meta-analysis from United Kingdom favoured use of IPLAI to reduce early postoperative pain after laparoscopic cholecystectomy.\[^{2}\] However, most of the studies included in this meta-analysis failed to document the effect of intraperitoneal local anaesthetic instillation on postoperative shoulder pain which is a well-recognised disturbing element with incidence of 30–50% in the postoperative period following laparoscopic cholecystectomy. The other strong point in our study is that the incidence of shoulder pain significantly reduced in intervention group (PE and PS) in comparison to control group. Such high incidence of shoulder pain in control group can be partly explained by the relatively prolonged duration of surgery and partly by the absence of IPLAI instillation.

In concordance with ours study, other investigators have also confirmed the superiority of pre-emptive analgesia in controlling post-operative pain.\[^{9,11}\] Several researchers used trocar site local anaesthetic infiltration as a form of pre-emptive analgesia. An American
study concluded that a simple combination of an oral nonsteroidal anti-inflammatory pain medication and preincision local anaesthetic infiltration is no better than placebo in controlling postoperative pain after elective laparoscopic cholecystectomy.\[12\] However, other studies using trocar site infiltration along with IPLA concluded favourably for pre-emptive analgesia. A Turkish study demonstrated that, trocar site local anaesthetic infiltration is more effective then IPLA instillation for postoperative analgesia and reduction in incidence of shoulder pain.\[8\] The authors explained that, higher incidence of shoulder pain in IPLA group could be because of dilution of IPLA with placement of a routine drain to observe potential bile leakages. The incidence of shoulder tip pain in our study is around 7–21% with IPLAI and very similar to the Turkish study (20%). This can be explained by the fact that unlike the Turkish study, we have excluded all the cases requiring insertion of a drain at the end of the surgery with a suspected spillage of bile or blood. Moreover, we have used a higher dose of IPLA (30 ml of 0.5% bupivacaine) in contrast to Turkish study (20 mL of 0.5% bupivacaine). A Canadian randomised control trial opined that a combination of pre-emptive periportal (20 mL) and intraperitoneal (40 mL of 0.25% bupivacaine with 1:200,000 epinephrine) infiltration provides superior quality analgesia compared to only post-operative IPLA or incisional local anaesthesia (LA) infiltration.\[13\] The recent Turkish\[14\] and Polish study\[15\] also emphasised the superiority of pre-emptive analgesia with intraperitoneal instillation of bupivacaine. In our study, we have used additional morphine (0.1 mg per kg) before incision as an alternative to periportal infiltration of LA in other studies to provide pre-emptive analgesia followed by IPLA instillation after creation of capnoperitoneum. Yet, our results are similar to their findings and suggest that a single dose of morphine before incision along with 30 mL of 0.5% bupivacaine IPLA instillation offers the same benefit of combined periportal and IPLA infiltration.

In our study, the superior quality and prolonged duration of postoperative analgesia does not got translated to attainment of early discharge criteria (modified PADSS 9/10) and time to attain this is comparable among our study cohort. This could be because the time to satisfy modified PADSS criteria was assessed only at two time points (8 AM and 6 PM) every day and not continually every hour. Hence, we might have missed few patients who have achieved the discharge criteria much earlier between 8 AM and 6 PM. However, on telephonic interview, the patients from pre-emptive group reported an early resumption to their daily activity in comparison to post surgery and control group.

Although we have taken care to standardise various factors (dose/concentration/site/position during IPLA instillation, volume of residual CO\(_2\)) except timing of instillation that might influence the benefits of IPLA instillation, one of the major limitation to this study is failure to differentiate and characterise the type of pain experienced by the patient while obtaining VAS score. Keeping in mind the multifactorial nature of pain after laparoscopic cholecystectomy, a nuanced analysis could have thrown some light on differential effect of pre-emptive and post-surgery IPLA instillation on different types of pain perception. The second limitation is we neither warmed the CO\(_2\) nor measured the residual CO\(_2\) volume at the end. However we have taken care to maintain intra-abdominal pressure between 12-14 mm Hg during laparoscopy and end-tidal carbon dioxide between 34-38 mm Hg just before extubation.

**CONCLUSION**

To conclude intra peritoneal local anaesthetic instillation immediately after creation of capnoperitoneum reduces the magnitude of postoperative pain, prolongs the duration of first analgesic request, reduces analgesic consumption, reduces incidence of shoulder pain in the postoperative period and facilitates early resumption of normal activity. The current regimen of IPLA instillation appears to be safe but warrant further study to ascertain plasma drug concentration before making its routine use as a part of multimodal approach to pain management.

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Conflicts of interest
There are no conflicts of interest.

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