Intra-peritoneal bupivacaine in management of post-operative shoulder tip pain following diagnostic laparoscopic procedure – a triple blind randomized control trial

A H M Makarim⁴, D M S T Gnanarathne⁵, S Hemapriya⁶

Abstract

**Background:** Post-operative shoulder-tip pain (STP) is a frequent complication following laparoscopy resulting in significant morbidity. This trial evaluates Intra-Peritoneal Bupivacaine (IPB) as a method of relieving post-operative STP.

**Methods:** Fifty-eight patients undergoing diagnostic laparoscopies were randomized to Group A (treatment) and Group B (control). Group A (n = 28) received 0.25% bupivacaine and Group B (n = 30) received an equal volume (10ml) of normal saline as an intra-peritoneal instillation in to the sub diaphragmatic space under direct vision. STP was recorded by using a visual analogue pain scale (VAS) at 0 hour, 4 hours, 8 hours of surgery, and at the time of discharge. Post-operative morbidity was assessed by additional analgesia and time taken for independent mobilisation.

**Results:** The incidence rate of STP in control group (B) was 70% while only 25% (7 out of 28) had reported STP in treatment Group (A), which is statistically significant (P = 0.001). Both severity of STP (P=0.004) and post-operative additional analgesia (P=0.001) were significantly higher in control group (B). Group A had an early mobilization (Mean Hours 9.43). Among the adverse effects studied, only nausea was reported higher in Group A (P<0.05).

**Conclusion:** Per-operative intra-peritoneal instillation with bupivacaine significantly reduces both frequency and severity of STP following diagnostic laparoscopy while improving post-operative morbidity.

Key words: shoulder tip pain, intra-peritoneal bupivacaine, laparoscopy, morbidity


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⁴ Senior Registrar in Obstetrics and Gynaecology, Castle Street Hospital for Women, Colombo, Sri Lanka.
⁵ Consultant Obstetrician and Gynaecologist, District Hospital Dickoya, Sri Lanka.
⁶ Consultant Obstetrician and Gynaecologist, General Hospital Kandy, Sri Lanka.

Correspondence: AHM, e-mail: <makarimlk@gmail.com>

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https://orcid.org/0000-0002-9311-7181

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Introduction
The occurrence of shoulder tip pain (STP) following laparoscopy varies from 35%-80% across patient populations in different studies1,2.
Mechanism of STP in laparoscopy was reviewed by Schoeffler, Diemunsch and Fourgeaud and they suggest rapid distension of peritoneum (due to introduction of CO\textsubscript{2}) possibly causes tearing of blood vessels and traumatic traction of the phrenic nerve. Hence, pain is perceived by releasing of inflammatory mediators3.
Several methods have been tried to reduce postoperative STP following laparoscopic procedures. Bilateral rectus sheath block performed at the level above the umbilicus with 15ml of 0.25% bupivacaine on each side4, application of local anaesthesia (lidocaine) under the diaphragm through a subphrenic catheter (but with conflicting results)5,11, spinal anaesthesia6 and NSAID analgesia7 are few of those methods. Some researchers even tried with introduction of normal saline to subphrenic space8.
The purpose of intra-peritoneal 0.25% Bupivacaine (IPB) administration is to block visceral nociceptive conduction by inhibiting sodium influx into nerve cells preventing depolarisation while providing an effective route of analgesia for postoperative shoulder tip pain9. Adverse reactions are rare when it is administrated correctly. Cardio toxicity when absorbed into systemic circulation and allergic reaction is not common. Other side effects are nausea, vomiting, vertigo, tinnitus, hypotension, bradycardia, and restless10. Literature review does not show that intra-peritoneal bupivacaine instillation is likely to mask the pain due to bowel perforation11,12.
Rationale and justification
Post-operative STP in laparoscopy is an important factor pertaining to morbidity according to the literature, as it causes shallow breathing of patient in immediate post-operative period which may result in reduced O\textsubscript{2} saturation in blood, atelectasis and even pneumonia5. We have no data to say how common is the STP following laparoscopy in Sri Lanka. While relieving such pain might improve morbidity including quick recovery. Hence, one might be able to do diagnostic laparoscopy as a ‘day-case surgery’ in Sri Lanka.

Materials and methods
This is an institution based triple-blind randomised controlled clinical trial. This study was conducted in Teaching Hospital Kandy.
Inclusion criteria
Those who admitted for diagnostic laparoscopic procedures (including Dye test) were recruited for this study.
Exclusion criteria
- BMI >25
- Patients who underwent laparoscopy but with extra interventions (such as adhesiolysis, cystectomy)
- Laparoscopic procedure extended more than 45 min.
Clear written information was given in all 3 languages and informed consent was taken on admission. Sample size was calculated according to V. Kasiulevicius & V. Šapoka14,
Sample size = \{P_1 (1-P_1) + P_2 (1-P_2)\} * f(\alpha,\beta)
(P_2-P_1)²
P1 & P2 – estimated outcome as proportion in control & treatment groups respectively
\(\alpha\) – type I error level (0.05)
\(\beta\) – type II error or statistical power (0.2)
f(\alpha,\beta) = 7.8489 (from the table)
According to the previous studies conducted, P1 & P2 are 28.6% and 63.3%. Therefore, sample size is 58. Of which cases are 28 (2 were excluded due to extension of surgery more than 45 min) and controls are 30. All patients were educated on how to use a visual analogue scale (VAS).
Simple randomisation was used by a computer-generated random number system (Excell-2010). Concealment was done by inserting the code into sealed opaque envelops by the House Officer. Envelopes were opened only after the anaesthesia by the Scrub Nurse and she prepared the syringe for instillation (either normal saline or bupivacaine accordingly). The patients were not aware about the group in which they belong to and the operator was not aware about the content of syringe. Hence, both the patient and the operator were blinded.

All laparoscopies were performed uniformly by the same operator with patients in modified Lloyd-Davies position under general anaesthesia. Pneumo-peritoneum was established by insufflation of $CO_2$ under constant 10 mmHg pressure and flow at a maximum of 3.5l/min. With 20 mmHg of pneumo-peritoneum, the scope was introduced through the primary port, and the procedure was carried-out with 15 mmHg of intra-abdominal pressure. After completion of procedure and before the removal of trocar, the laparoscopic injector (aspiration needle see Figure 1) was used for instillation of either 0.25% Bupivacaine (Group A) or normal saline (Group B) in to sub diaphragmatic space under direct vision. The volume of bupivacaine was calculated according to the body weight (2 mg/kg, 2.5 mg per ml in 0.25% vial). Group B received equal volume of normal saline. Since the injector can retain about 6 ml of fluid, we flushed it with equal amount of sterile distilled water (6 ml) after the dose of either bupivacaine or normal saline. Then the residual $CO_2$ was evacuated. Local infiltration of bupivacaine (2.5 ml of 0.25%) was given to entry site in both groups identically to mask the pain due to entry site wound. Post-operative care was given uniformly to both groups according to the unit protocol.

Figure. Consort chart of the trial

Figure 1. Laparoscopic aspiration needle.
Zero hour (0 hr) was taken as the time of arrival to the ward following surgery and the STP was assessed using the VAS at 0 hr, 4 hr, and 8 hr and on discharge (pain at discharge was assessed at ‘24 hours from 0 hour’). Those patients who had VAS > 4, were administered diclofenac suppository (50 mg) as rescue analgesia. Resident doctors were involved in entering the pain intensity by the VAS (they were unaware about the intervention made). “Additional analgesia” was referred when the consumption of diclofenac Na exceeds 2 or more times by the patient during 24 hours of procedure.

In analysis of side effect profile of bupivacaine, vomiting, nausea and systolic hypotension were taken into consideration. Here, vomiting of 2 or more was considered and hypotension was defined as more than 15mmHg drop of post-operative systolic blood pressure from pre-operative value, which was monitored hourly for 8 hours from 0 hour by calibrated automated blood pressure device. Patients were asked to grade the severity of nausea (1, 2, or 3) and grade 3 was marked as ‘nausea +’.

**Outcome measures**

Primary outcome measures were incidence of post-operative STP and severity of pain. Secondary outcome measures were morbidity of patients in terms of hospital stay (in hours), side effect profile of bupivacaine and use of additional analgesics in post-operative period.

**Statistical analysis**

Incidence of STP (VAS >4 is considered as ‘Yes’) was calculated as proportions and compared. Here null hypothesis was formulated as there is no difference in proportion of occurrence in pain in both groups. Then hypothesis was tested for significance. Chi square test was used and P value <0.05 was taken as statistically significant.

Severity of STP in both groups were analyzed by the Student T test (unpaired). ‘Additional analgesic consumption’ was analyzed by two sample proportion tests and compared. Further, the Mann-Whitney U-test was used to analyze ‘hours of hospital stay’ and ‘side effect profile of bupivacaine’. SPSS Version 21 was used for analysis.

**Ethical consideration**

Ethical approval of the study was obtained from ethical review committee of Teaching Hospital Kandy.

**Results**

58 patients were randomized to Group A and 30 patients were randomized to group B.

**Table 1. Demographic and surgical data (Mann-Whitney U test)**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in yrs)</td>
<td>30.85±4.17</td>
<td>31.57±4.98</td>
<td>0.695</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.5±2.2</td>
<td>23.0±2.5</td>
<td>0.361</td>
</tr>
<tr>
<td>Duration of lap (min)</td>
<td>30.0±5.8</td>
<td>32.2±6.0</td>
<td>0.717</td>
</tr>
</tbody>
</table>

There is no statistical difference in age, BMI and duration of laparoscopic procedure among 2 groups tested in this study (P>0.05).

**Table 2. Overall incidence of STP**

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=28)</th>
<th>Group B (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>7 (25.0%)</td>
<td>21 (70.0%)</td>
</tr>
<tr>
<td>No pain</td>
<td>21 (75%)</td>
<td>19 (30%)</td>
</tr>
</tbody>
</table>

Overall, only 7 out of 28 (25%) in Group A and 21 out of 30 (70%) in Group B had the STP which is statistically highly significant (P=0.001) according to Chi square test.

Table 3 shows that significant pain occurs at 4 and 8 hours in both groups.

**Table 3. Pain at different times**

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=28)</th>
<th>Group B (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Hours</td>
<td>1 (3.6%)</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>4 Hours</td>
<td>7 (25%)</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>8 Hours</td>
<td>3 (10.8%)</td>
<td>15 (50.0%)</td>
</tr>
<tr>
<td>Discharge</td>
<td>0</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Overall</td>
<td>7 (25.0%)</td>
<td>21 (70.0%)</td>
</tr>
</tbody>
</table>
Post-operative morbidity

This was assessed by additional analgesic consumption, early mobilization and side effect profile of bupivacaine.

### Table 4. Severity of STP (Student’s T test)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean VAS</th>
<th>SD (Standard Deviation)</th>
<th>SEM (Standard error of Mean)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>28</td>
<td>3.86</td>
<td>1.53</td>
<td>0.290</td>
<td>0.004</td>
</tr>
<tr>
<td>Group B</td>
<td>30</td>
<td>6.21</td>
<td>1.83</td>
<td>0.346</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Severity of STP following laparoscopy among 2 groups were compared by unpaired T test for significance and there is a significant higher severity of pain was reported in Group B (P=0.004).

### Table 5. Additional analgesic consumption

<table>
<thead>
<tr>
<th>Additional analgesia</th>
<th>Group A</th>
<th>Group B</th>
<th>Chi square test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not given</td>
<td>21</td>
<td>10</td>
<td>P=0.003</td>
</tr>
<tr>
<td>given</td>
<td>7</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Additional analgesic consumption after the laparoscopy was significantly high (Chi square test) in Group B (P-value 0.003).

### Table 6. Side effect profile

<table>
<thead>
<tr>
<th>Side effect profile</th>
<th>Group A</th>
<th>Group B</th>
<th>T-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>No side effects</td>
<td>10</td>
<td>22</td>
<td>P=0.013</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>1</td>
<td>P=0.374</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2</td>
<td>1</td>
<td>P=0.423</td>
</tr>
</tbody>
</table>

Nausea was the only side effect seen significantly higher in Group A (P < 0.05).

### Table 7. Hospital stay (in hours) (Chi Square test)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean (hours)</th>
<th>SD</th>
<th>SEM</th>
<th>Sig (2-tailed T-Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>28</td>
<td>9.43</td>
<td>2.008</td>
<td>0.379</td>
<td>0.002</td>
</tr>
<tr>
<td>Group B</td>
<td>30</td>
<td>13.36</td>
<td>2.984</td>
<td>0.564</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Here, the time taken to mobilize independently from the bed was calculated as ‘Hospital stay’ in hours. However, all patients were kept for at least 24 hours from the laparoscopy to complete the study protocol.

When this is analyzed by chi-square test, \([X^2\text{ value}=23.26, P=0.001, \text{OR}=22 (95\%\ CI 5.47-88.42)]\), patients who were given bupivacaine are at least 5.47 times likely to be discharged early than not given. Hence, bupivacaine has significantly shortened the post-operative hospital stay.

**Table 8. Sub-group analysis (Cross-tabulation)**

<table>
<thead>
<tr>
<th>Duration of stay</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 10 hours</td>
<td>85.7% (24)</td>
<td>23.26% (7)</td>
</tr>
<tr>
<td>&gt;10 hours</td>
<td>14.3% (4)</td>
<td>76.7% (23)</td>
</tr>
</tbody>
</table>

Outside this study, usually most of our patients do not complain of STP. Because they may think this is ‘normal’ after the procedure or complain as ‘non-specific pain’. This might be one of the reasons why we do not see STP as common as reported.

Mean post-operative hours confined to bed in Group A and group B were 9.40 and 13.30 respectively (\(P=0.002\)). Approximately 85\% of patients in Group A got out of bed independently before 10 hours, while only 23\% in Group B was able to do so. Hence, those who were given bupivacaine is at least 5 times more likely to mobilize (discharge) earlier than control (95\% CI 5.47-88.42).

One fourth of patients in Group A and two third of patients in Group B had taken additional analgesia (as diclofenac Na 50 mg suppositories) within 24 hours of procedure. Both percentages were compared by T-Test and there was again significant increase in need of analgesia in control group (\(P=0.003\)).

In order to assess the side effect profile of bupivacaine, nausea, vomiting and hypotension (which are more frequent adverse effects of bupivacaine reported in literatures\(^{10}\)) are analyzed. Bupivacaine group had significantly higher incidence of nausea (\(P=0.006\)) than control group, while other side effects were similar in both groups. Even though, nausea is non-specific symptom, it is the commonest side effect of bupivacaine in our study.

There were no demographic factors influencing the incidence of STP such as age and BMI. According to the previous works, residual gas left-in situ, time of procedure and intra-abdominal pressure might have influenced the incidence of STP\(^{11}\), but these factors were minimized by randomization and maintaining the uniformity in both groups.
Main limitations encountered in this study are, previous abdominal surgeries were not considered as a confounding factor in analysis, only STP was asked, intervened and analyzed but other post-operative pain might influence the perception of STP and long-term implications were not studied if any.

Conclusion and recommendation

STP is very common following laparoscopy (70%) and this might adversely affect short term morbidity. IPB is an effective, and safer method to relieve post-operative STP without any significant side effects. IPB has reduced post-operative additional analgesic consumption and enable early mobilization. We recommend to conduct similar type of study in operative laparoscopies and review them at regular set-interval to analyze long-term complications if any. It would be much better to include a Patient Satisfaction Questionnaire in future studies to express their views and experience to understand the fact further.

References


