Post-operative pain after laparoscopic ventral hernia repair, the impact of mesh soakage with bupivacaine solution versus normal saline solution: A randomised controlled trial (HAPPIEST Trial)

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Abstract

Background and Aims: Early postoperative pain after laparoscopic ventral hernia repair remains a concern for patients. Local application of anaesthetic agent in the surgical dissection area can potentially overcome this problem. The objective of this study was to evaluate the impact of soaking mesh in 0.5% bupivacaine solution as compared to normal saline solution on the post-operative pain.

Methodology: We conducted a parallel-design double-blind randomised controlled trial. Adult patients with uncomplicated ventral abdominal wall hernias were included in the trial. Mesh was soaked in 0.5% solution of bupivacaine before application in patients in the intervention arm, whereas it was soaked in normal saline solution for patients in the control arm. Post-operative pain was assessed by trained staff at 6 h and 24 h from surgery. It was graded on visual analogue scale (VAS) from 0 to 10.

Results: Trial was conducted from 16 November, 2015, to 15 September, 2017. During the study period, a total of 114 patients were randomised. Nine patients were excluded after randomisation. A total of 55 patients were analysed in the intervention arm and 50 patients were analysed in the control arm. Mean pain score at VAS at 6 h after laparoscopic ventral hernia repair in the intervention arm was 5.05 ± 1.2, whereas in the control arm, it was 5.54 ± 1.1 and the difference was statistically significant (P = 0.03-independent sample t-test). Mean pain score at VAS at 24 h after laparoscopic ventral hernia repair in the intervention arm was 3.16 ± 1.2, whereas in the control arm, it was 3.58 ± 1.4 and the difference was not statistically significant (P = 0.11-independent sample t-test).

Conclusion: Soakage of mesh in 0.5% bupivacaine solution before application in laparoscopic ventral hernia repair significantly reduces early post-operative pain.

Keywords: Bupivacaine, laparoscopic surgery, local anaesthetics, mesh repair, post-operative pain, ventral hernia

Trial Registration: Trial was registered with clinicaltrials.gov (NCT03035617)

URL: https://clinicaltrials.gov

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Submitted: 25-Feb-2019, Accepted in Revised Form: 13-Mar-2019, Published: 16-Jan-2020

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How to cite this article: Chawla T, Shahzad N, Ahmad K, Ali JF. Post-operative pain after laparoscopic ventral hernia repair, the impact of mesh soakage with bupivacaine solution versus normal saline solution: A randomised controlled trial (HAPPIEST Trial). J Min Access Surg 2020;16:328-34.
INTRODUCTION

Laparoscopic approach to uncomplicated ventral hernia repair as compared to open repair has advantages of less post-operative pain, reduced risk of wound infection, early recovery, short hospital stay and decreased overall cost of treatment. Patient satisfaction after laparoscopic procedure is also better as compared to open repair. Despite multiple advantages of the laparoscopic approach, it is utilised in only about quarter of patients with ventral hernia in developed countries. Early post-operative pain and discomfort after laparoscopic repair remain a concern for patients requiring prolonged hospital stay and parenteral narcotic analgesics. This quite often proves to be a hindrance in early ambulation, enhances patient discomfort and prevents early discharge from hospital. Early post-operative pain is thought to be secondary to dissection in the area of mesh application. Local application of anaesthetic agent in this area can potentially overcome this problem and make the procedure feasible as an ambulatory care operation.

Local anaesthetics infiltration at the wound site after various procedures is known to be effective in reducing immediate post-operative pain. In the case of laparoscopic ventral hernia repair, delivering local anaesthetic at the site of mesh application can be achieved by soaking the mesh in local anaesthetic solution before application. Bupivacaine is long-acting local anaesthetic which if used for analgesia purpose is known to be effective up to 15 h. Results of studies that have used this bupivacaine intraperitonealy in other types of surgeries for the analgesic purpose have shown it to be safe. Till date, there is no evidence regarding the impact of soaking mesh in bupivacaine solution before application in the case of laparoscopic ventral hernia repair.

Objective

Primary objective
The primary objective is to evaluate the impact of impregnating mesh in 0.5% bupivacaine solution as compared to normal saline solution on the post-operative pain after laparoscopic ventral hernia repair.

Secondary objective
The secondary objective is to evaluate the impact of impregnating mesh in 0.5% bupivacaine solution as compared to normal saline solution on the length of hospital stay after laparoscopic ventral hernia repair.

METHODOLOGY

This trial was named Hernioplasty And Post-operative Pain after Impregnating mESh with Topical anaesthetic (HAPPIEST) trial.

Study design
We conducted a parallel-design, double-blinded randomised controlled trial having 1:1 ratio of patients in intervention and control arms.

Selection criteria

Inclusion criteria
Adult patients both males and females of age 16 years and above who presented with ventral abdominal wall hernia and were scheduled to undergo laparoscopic repair were eligible to be included in the trial.

Ventral abdominal wall hernia was defined as defect in the anterior abdominal wall through which contents of the abdominal cavity could protrude. The anterior abdominal wall extends from xiphisternum above to symphysis pubis below and anterior axillary lines laterally.

We included patients with both primary (umbilical, paraumbilical and epigastric hernias) and incisional hernias in our study.

Exclusion criteria
- Complicated ventral abdominal wall hernia (strangulated, obstructed)
- Recurrent hernias
- Renal insufficiency: Serum creatinine >1.5
- Hepatic insufficiency: Known case of chronic liver disease or total bilirubin >2 mg/dl
- Pregnant or lactating females
- Emergency operations
- Current or regular use of analgesics for some other indication
- Patients with known hypersensitivity to bupivacaine
- Refusal to participate in the study
- Simultaneous additional surgical procedures.

Settings
The study was conducted in the general surgery unit of our hospital. Patients were evaluated in clinic at the time of presentation regarding eligibility to participate in the study.

In both arms, operative procedure of laparoscopic ventral hernia repair was the same except solution used to soak the mesh before application. In control arm, mesh was...
soaked in normal saline solution, whereas in intervention arm, mesh was soaked in 0.5% bupivacaine solution before application. Solution adsorption to the mesh was corresponding to the size of the mesh.

**Outcome measures and assessment**

**Post-operative pain**

Post-operative pain was assessed by trained staff. Pain was graded on visual analogue scale (VAS).\(^1\)\(^4\) VAS is validated scoring system according to which intensity of pain is scored on a scale of 0–10, 0 being no pain and 10 being worst pain. Scale is as shown in annexes II. Scale was presented to the participants at 6 and 24 h post-procedure. They were required to mark appropriate score on that scale according to the severity of their pain. After the operation, the first assessment of pain was made 6 h postoperatively. The second assessment was made at 24 h from the end of the operation. This assessment was made face-to-face if the patient was admitted in the hospital or on the telephone if patient got discharged.

Postoperatively, two doses of intravenous paracetamol were given at interval of 6 h starting 3 h after the end of the operation. Intravenous tramadol was given on as per required basis on request of patient in dose of 50 mg with gap of at least 8 h. Number of times additional tramadol required was recorded.

**Length of hospital stay**

Length of hospital stay was taken in number of days from the day of operation. It was divided into two categories as day case surgery and one or more days stay in the hospital.

**Sample size**

Sample size was calculated using the World Health Organisation software for sample size calculation. Muysoms et al. in 2013 reported pain after laparoscopic ventral hernia repair after various mesh fixation techniques on VAS ranging from 0 to 10.\(^1\)\(^3\) They reported pain after fixation with metallic tacks to be 4.4 ± 2.3 at 4 h. We hypothesised that bupivacaine soakage of mesh would reduce this pain by at least on third as compared to soakage with normal saline solution. A minimum of 44 patients were required in each group keeping the level of significance of 5% and power of the study to be 90%. Anticipating 10% loss to follow-up, we planned to include 50 patients in each group.

**Interim analysis**

We conducted one interim analysis in mid of trial. At the time of interim analysis, criteria to stop trial were defined as value of \(P < 0.025\) for the outcome of interest or <0.05 for adverse events related to the intervention.

There was no statistically significant difference in post-operative pain at 6 and 24 h (\(P = 0.077\) and 0.097, respectively) and no adverse event noted. Hence, trial continued till its completion.

**Randomisation**

The process of randomisation and allocation concealment was carried out by Institutional Clinical Trial Unit (CTU). Block randomisation technique was utilised in this trial. Blocks each comprising 10 participants were made. In each block, random allocation sequence was generated using computer-generated random numbers which was kept undisclosed to the investigators, patients and outcome assessors. After the assessment of participation in the clinical trial, CTU was informed about the scheduled day and time of operation. Half-an-hour before the operation, normal saline solution or 0.5% bupivacaine solution was provided by CTU in coded form according to treatment arm allocation. Records of the codes were kept by the CTU. Both solutions were transparent and had no smell. Participants, investigators and outcome assessors were not aware of the allocation.

**Co-variates**

Information was obtained about covariates on a specifically designed questionnaire. These include:

- Age – Number of years from birth
- Gender of the participants
- Pre-operative pain – Pre-operative pain was recorded on VAS as the pain without having any analgesic medications
- Number of tacks and sutures applied during operation to fix the mesh
- Size of mesh used
- Size of hernia defect – Maximum diameter in centimetres
- Duration of operation in number of minutes from incision to dressing.

**Operative procedure**

Laparoscopic ventral hernia repair is performed under general anaesthesia. The laparoscopic approach to repair ventral hernia at our institution involves transabdominal approach through three laparoscopic ports inserted on one side of the abdomen. Suture closure of defect varies from surgeon to surgeon. Composite mesh is applied to the anterior abdominal wall after reducing hernia contents. Mesh used at our institution (Parietex™ Composite Mesh) for ventral hernia repair comprises two layers, peritoneum side layer of polyester and abdominal cavity side of absorbable collagen film. Mesh is soaked in saline before insertion into the peritoneal cavity. Mesh is applied using
metallic tacks. Sutures are also applied at four corners of the mesh.

Use of local anaesthetics at the sites of ports insertion and transfacial sutures varies from surgeon to surgeon. When local anaesthetics were used for port and suture sites for patients registered for trial, dose adjustment was done to avoid maximum allowed dose presuming the patient to be in the intervention arm.

**Monitoring for adverse drug reactions**

Bupivacaine is long-acting local anaesthetic drug. Although minimum toxic dose of bupivacaine for intra-peritoneal use is not defined, the analgesic effect of its intra-peritoneal use, especially after laparoscopic cholecystectomy, has been assessed in several interventional studies. Intra-peritoneal use of up to 50 ml of 0.25%\(^{[12,16,17]}\) or up to 20 ml of 0.5% solution has not shown any drug-related adverse reactions.\(^{[18]}\)

Known serious adverse reactions of bupivacaine after use as local anaesthetic are due to its high serum concentrations after use, commonly seen after accidental administration directly into blood vessels. These are reported to be effects on the central nervous system such as seizures and convulsion and cardiac effects such as arrhythmias and heart block. These adverse reactions are noted in 1:1000 cases.\(^{[19]}\) Time to onset of these adverse effects ranges from a few seconds to up to 1 h.\(^{[20]}\) We monitored trial participants for these adverse effects for up to 1 h after surgery in the operating room and recovery room.

**Ethical considerations**

Approval was sought from the Ethics Review Committee (ERC) before the start of the trial (Approval Number: 3159-SUR-ERC-14). Written informed consent was provided by the participants before inclusion in trial. Trial was registered with clinicaltrials.gov with registration number NCT03035617.

**Statistical analysis**

We conducted intention to treat analysis. Quantitative variables are reported as mean ± standard deviation. Qualitative variables are reported as numbers and percentages. Distribution of co-variates among two arms is tested using the Chi-square test or independent sample t-test for qualitative and quantitative variables, respectively. Independent sample t-test is applied to test the impact of the use of bupivacaine solution as opposed to normal saline solution on post-operative pain as measured by VAS. The Chi-square test is used to test the impact of intervention on the length of hospital stay.

The work has been reported in line with consolidated standards of reporting trials guidelines.

**RESULTS**

Trial was conducted from 16 November, 2015 to 15 September, 2017. During the study period, a total of 161 patients were evaluated for inclusion into the study. Forty-seven patients were excluded due to various reasons as given in Figure 1. A total of 58 patients were randomised to the intervention arm and 56 patients were randomised to control arm. After exclusions for various reasons as given in Figure 1, 55 patients were analysed in intervention arm and 50 patients were analysed in the control arm. Demographic and disease related details of the patients in both arms are given in Table 1.

Mean pain score at VAS at 6 h after laparoscopic ventral hernia repair in the intervention arm was 5.05 ± 1.2, whereas in the control arm, it was 5.54 ± 1.1 and the difference was statistically significant (\(P = 0.03\)-independent sample t-test).

Mean pain score at VAS at 24 h after laparoscopic ventral hernia repair in the intervention arm was 3.16 ± 1.2, whereas in the control arm, it was 3.58 ± 1.4 and the difference was not statistically significant (\(P = 0.11\) – independent sample t-test).

Length of hospital stay was not statistically significant among two groups. Overall 9 (16.4%) patients went

**Table 1: Demographics and other variables distribution among both groups**

| Variables                          | Intervention arm (n=55) | Control arm (n=50) | P Value |
|-----------------------------------|------------------------|--------------------|---------|
| Gender (male)                     | 13 (23.6)              | 9 (18.0)           | 0.48    |
| Diabetes mellitus                 | 9 (16.4)               | 12 (24)            | 0.33    |
| Type of hernia                    |                        |                    |         |
| Primary                           | 9 (16.4)               | 12 (24)            | 0.33    |
| Incisional                        | 46 (83.6)              | 38 (76.0)          |         |
| Site of hernia                    |                        |                    |         |
| Umbilical/paraumbilical           | 50 (90.9)              | 42 (84.0)          | 0.55    |
| Midline other than umbilical/paraumbilical | 4 (7.3)               | 6 (12)             |         |
| Paramedian                        | 1 (1.8)                | 2 (4)              |         |
| Method of fixation                |                        |                    |         |
| Tacks only                        | 14 (25.5)              | 10 (20)            | 0.51    |
| Tacks and sutures                 | 41 (74.5)              | 40 (80)            |         |
| Suture closure of hernia defect   | 10 (18.2)              | 11 (22)            | 0.63    |
| Age (years)                       | 47.5±12.6              | 49.9±11.3          | 0.31    |
| Maximum diameter of defect (cm)   | 3.7±2.6                | 4.3±3.0            | 0.23    |
| Size of mesh (area in cm\(^2\))   | 217.7±101.7            | 252.0±93.9         | 0.08    |
| Number of tacks/tacks plus sutures| 34.8±12.0              | 37.4±13.9          | 0.30    |
| Operative time (min)              | 75.6±35.7              | 80.4±39.4          | 0.52    |
| Additional doses of tramadol needed| 2.5±1.3               | 2.5±1.0            | 0.97    |

\(\text{SD: Standard deviation}\)
home the same day in intervention arm, whereas in control arm, 5 (10%) patients went home the same day ($P = 0.338$ – Chi-square test).

No drug-related adverse events occurred in the trial participants.

**DISCUSSION**

Although the use of local anaesthetics to control post-operative pain is widely recommended,[21] its use through soaking of mesh in laparoscopic ventral hernia repair has not been evaluated through randomised controlled trial. Results of this trial demonstrate that soaking of mesh with bupivacaine solution before application in laparoscopic ventral hernia repair confers the advantage of better early post-operative pain control. This smoothens the recovery from the operation and improves patients’ satisfaction.[22] Adequate pain control also helps in early mobilisation and early discharge from the hospital,[23] which, in turn, can potentially reduce the cost of care and burden on healthcare. Furthermore, intra-abdominal use of single-dose bupivacaine has much less risk of introducing infection as compared to injecting via continuous infusion catheters or transcutaneous injections at surgical sites.

Pain after laparoscopic hernia repair is thought to originate from compression or injury to tissues from mesh itself or tacks used to fix it.[11] Variations in mesh fixation methods have been evaluated in multiple studies, some demonstrating increased pain with helical tacks[24] while others show that pain after transfascial sutures is more.[15]

Most of the literature relates to chronic pain after hernia repair and its management. Local anaesthetic infiltration of ports and sutures sites is shown to be effective for laparoscopic procedures and open operations.[21] Similarly, trial conducted by bellows cystic fibrosis demonstrates improved pain control, but no effect on analgesics requirement when local anaesthetic infiltration is done at suture site.[11] In our trial, instillation of local anaesthetic at port and suture site was at the discretion of the operating surgeon. Considering the design of the study, effect if any on post-operative pain would not have confounded the results due to random allocation and blinding.

Furthermore, the number of tacks used in mesh fixation has not consistently correlated with the amount of post-operative pain.[25] A recent meta-analysis concluded...
that no fixation method is superior to the other for post-operative pain control.\[26\] On the other hand, chronic pain after hernia repair can often be quite troublesome.\[9\] Whether control of early post-operative pain using bupivacaine would have any impact on long term pain relief is not known.

Local anaesthetics have been shown to be safe for intra-peritoneal use,\[27\] and are routinely used in some centres to reduce post-operative pain after laparoscopic cholecystectomy.\[28\]

Although our results have not shown any significant advantage of this intervention in reducing the length of hospital stay or reduction in the use of analgesics, studies with sample size calculated specifically for this purpose are needed. Any potential bias arising as a result of the Hawthorne effect (participants being aware of pain being monitored) was controlled by the blinding of participants to treatment arm allocation. Hence, any effect would have impacted both arms equally.

**CONCLUSION**

Soakage of mesh in 0.5% bupivacaine solution before application in laparoscopic ventral hernia repair significantly reduces early post-operative pain.

**Acknowledgements**

The authors would like to thank Miss. Shagufta Maqsood, Data Collector for the study.

**Financial support and sponsorship**

This work was financially supported by the University Research Council at The Aga Khan University Hospital Karachi. (URC Grant Number: PF 63/1214).

**Conflicts of interest**

There are no conflicts of interest.

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