ORIGINAL ARTICLE

Laparoscopic versus open adhesiolysis for adhesive small bowel obstruction (LASSO): an international, multicentre, randomised, parallel, open-label trial

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Abstract

Background

Although laparoscopic adhesiolysis for adhesive small bowel obstruction are being undertaken more frequently, widespread acceptance is lacking because supporting evidence is limited and there is a concern regarding its benefits.

Methods

In an international, multicenter, parallel, open-label trial, we randomly assigned 104 patients who had adhesive small bowel obstruction not resolving by conservative means to undergo either open or laparoscopic adhesiolysis (allocation ratio 1:1) using sealed envelope method between July 2013 and April 2018. The study was conducted in five academic university and three community (central) hospitals in two countries (Finland and Italy). We designed key exclusion criteria to include only patients with high likelihood of single adhesive band into the trial. The primary outcome was postoperative length of stay assessed at time of discharge. Key secondary outcomes were complications within 30 days, return of bowel function during the hospital stay, postoperative pain within 7 postoperative days, length of epidural catheter during the hospital stay, use of opioids during the hospital stay, and length of sick leave (assessed at the end of the sick leave). This trial was registered with ClinicalTrials.gov, number NCT01867528.

Findings

One hundred patients were included in the modified intention-to-treat analyses (49 in the open surgery group and 51 in the laparoscopy group). The postoperative length of stay for open group was on average 1·3 days longer than that in laparoscopy group (geometric mean 5·5 (range 2 – 19)

versus 4·2 (range 1 - 20), ratio of geometric means 1·31 (95% confidence interval 1·06 – 1·61), p = 0·013). The rate of complications (21 (43%) vs. 16 (31%), p = 0·23, OR 0·61 (95% CI 0·27 – 1·38)) was similar between open and laparoscopic groups, respectively. Time from surgery to bowel function was shorter in laparoscopy group (geometric mean 41 hours) than in open group (geometric mean 63 hours) (ratio of geometric means 1·54 (95% CI 1·11 – 2·11), p = 0·007). Pain was lower in laparoscopy group on day 3 (median of daily mean pain of visual analog scale 2 (IQR 1 – 3) versus median 1 (IQR 0 – 2), p = 0.006, r = 0.32) and day 4 (median 1.5 (IQR 0·5 – 3) versus 0·5 (IQR 0 – 1·5), p = 0·015, r = 0·32) compared to open group, respectively. The length of epidural catheter was longer in open group than in laparoscopy group (median 39 hours (IQR 0 – 54) versus median 0 hours (IQR 0 – 0), p < 0·001, r = 0·51). Opioid use was similar between the groups (median milligrams of morphine equivalent per day 5·7 (IQR 1·0 – 12·0) in open group versus 3·6 (IQR 0 – 12·2) in laparoscopy group, p = 0·47, r = 0·07). The length of sick leave was on average 12 days longer in open group than in laparoscopy group (geometric means 24 days (n = 10) versus 12 days (n = 11), ratio of geometric means 1·90 (1·03 – 3·51), p = 0.04). One patient died in both group within 30 days. Surgery in 13 patients (25%) in laparoscopic group were converted to open surgery.

Interpretation

Laparoscopic adhesiolysis provides quicker recovery in selected patients with adhesive small bowel obstruction.

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Introduction

Small bowel obstruction is a common surgical emergency, and adhesions are the most common cause.[1,2] While (suspicion of) strangulation requires immediate operative treatment, initial management of non-strangulated adhesive small bowel obstruction consists of non-operative treatment by decompressing the bowel, restoring fluid balance, and a trial using oral water-soluble contrast media to stimulate the bowel and resolve obstruction.[3] Yet, a significant proportion will need surgery to relieve the obstruction. As a standard, surgery has been performed via laparotomy to obtain wide field for safe adhesiolysis. Recently, use of laparoscopy has increased in several visceral operations, and even complex elective procedures are nowadays being performed.[4-6] The feasibility, increase in expertise, and excellent results of these elective laparoscopic procedures have led to push the boundaries in emergency laparoscopic surgery.

Laparoscopic approach for small bowel obstruction is theoretically controversial. On one hand, it is ideal approach, as the adhesion causing the obstruction is often only a single band and the objective of the operation is just to cut that band. On the other hand, obstructed small bowel is dilated and fragile, and fills the abdominal cavity leaving little room to move instruments making the procedure technically demanding.

Pooled analyses of non-randomized series suggest significant reductions in mortality, morbidity, wound infections, and length of hospital stay by using laparoscopic approach instead of open surgery.[7-10] It is acknowledged that these series have high risk of bias owing to obvious selection of less severe cases to laparoscopic approach.[10,11] Although laparoscopic approach is used more frequently than before,[12,13] it has not gained widespread acceptance. Only 50-60% of surgeons would consider using laparoscopy for small bowel obstruction in surveys carried out in the UK and Connecticut.[14,15] The lack of widespread adoption can be appointed to three major reasons: laparoscopic adhesiolysis is technically demanding,[3] it has been associated with higher

risk of iatrogenic bowel injury, [12] and, to our knowledge, there is no randomised evidence of benefit and safety.[8,10,11,13]

Because of controversy regarding the safety and benefits of laparoscopic adhesiolysis over open approach for small bowel obstruction, we conducted LAparoscopic versuS open adhesiolysis for adhesive Small bowel Obstruction (LASSO) trial. The main hypothesis was that laparoscopic adhesiolysis is feasible treatment of adhesive small bowel obstruction, and it shortens the length of hospital stay without increasing morbidity. This publication reports primary and secondary (short-term) outcomes, while tertiary (long-term) outcomes will be reported when 5-year follow-up will be available.

Methods

Study design and participants

The LASSO trial was an international, multicenter, open-label, parallel group, individually randomised superiority trial comparing laparoscopic approach to open surgery in patients with acute adhesive small bowel obstruction that was not resolved by conservative means. The trial was conducted in five academic university and three community (central) hospitals in two countries (Finland and Italy). The trial was registed prior commencement at ClinicalTrials.gov (NCT01867528). The full protocol of the trial has been published earlier.[16] The trial protocol was approved by ethical committee of the Helsinki University Hospital, and also by the institutional review boards at each site.

Patients with clinical and radiological (computed tomography) signs of acute adhesive small bowel obstruction were eligible. As adhesive small bowel obstruction has a high tendency to resolve without surgery, patients underwent a trial of conservative therapy prior inclusion in the trial: nasogastric tube was inserted, patients were admitted to surgical ward and if no signs of

resolving obstruction were present after 12 hours, an oral water-soluble contrast (Gastrografin®) was administered. After at least eight hours wait an abdominal x-ray was taken, and if the contrast had not advanced to colon, the obstruction was deemed not to resolve by conservative means. If Gastrografin® was contraindicated (e.g. allergy) or not available, a 48-hour conservative treatment was required to deem conservative means ineffective i.e. there were no signs of bowel function and there was significant secretion into the nasogastric tube.

Patients who had an anesthesiological contraindication, age below 18 years or over 95 years, pregnant, living in institutionalized care, and with a hospital stay more than one week prior to surgical consultation were excluded from the trial. Patients with suspicion of either strangulation or peritonitis were excluded because immediate operative treatment was necessary. In addition, patients who had undergone bariatric surgery were excluded as there is a wide consensus that these patients should be operated laparoscopically. As the complexity of adhesions causing small bowel obstruction are impossible to estimate clinically or radiologically, we introduced several exclusion criteria in order to select patients that would have a high likelihood of having a single adhesive band causing the obstruction. We hypothesized that by including only patients with single adhesive band, and thus technically easy cases for laparoscopic adhesiolysis, we could keep the conversion rate to open surgery at minimum. Exclusion criteria are shown in patient selection flow chart (Figure 1). All patients gave written informed consent to participate in the trial.

Randomisation and masking

Patients were randomly allocated in a 1:1 ratio to undergo open or laparoscopic adhesiolysis. The randomisation sequence was generated using Blockrand 1.1 package with R statistical software (R Foundation for Statistical Computing, Vienna, Austria). A block randomisation with randomly

varying block size (2, 4, or 6) was stratified according to center. The information regarding block size was openly stated in the protocol, but as it was randomly varied, the persons recruiting patients were not aware which of the varied block size was used at that particular point of time. The randomisation sequence was concealed in an opaque numbered envelopes by a person not part of the trial. The recruiters, treating physicians, researchers, and patients were unaware of the randomization sequence. Patients were randomised by opening the sealed envelope containing the assigned group. As this was an open-label trial, patients, care providers, outcome assessors, nor data analyst were not blinded.

Procedures

Fluid balance and electrolyte distrurbances were corrected preoperatively and prophylactic antibiotics (cefuroxime 1500mg and metronidazole 500mg) were administered just before incision. Epidural catheter was inserted if deemed necessary by the anesthesiologist.

For open surgery, midline incision was used, adhesions were dissected and fascia and skin closed. For laparoscopic approach a standardized method was instructed. Small bowel was examined starting from terminal ileum with meticulous care taken not to grasp or harm the dilated small bowel. To maintain safety, prespecified criteria for conversion to open surgery were created: 1) confirmed or suspected small bowel perforation, which is not amenable for laparoscopic suturing, 2) a transition site is not identified, 3) the reason for obstruction is not found, 4) peritoneal carcinosis is detected, 5) the presence of widespread diffuse adhesions, and 6) need for bowel resection. All surgeons performing either open or laparoscopic surgery were required to have solid experience and skills for complex laparoscopic procedures, and needed to have performed at least two laparoscopic adhesiolysis prior operating on patients randomised in

the trial. The operating surgeon was the on-call surgeon, or the center's investigator. These qualified surgeons were allowed to perform both open and laparoscopic procedures.

Postoperative care was also standardised with following instructions: Nasogastric tube was instructed to be kept in place until secretion was less than 500 ml per eight hours. After removal of the nasogastric tube, the patient was allowed to drink up to 200 ml per every six hours. Thrombosis prophylaxis and proton pump inhibitors were used during the hospital stay. Only ibuprofen, paracetamol, tramadol, and oxycodone were used for pain, in addition to possible wound or epidural catheter. There was no specific guidance in the study protocol for early mobilisation or physiotherapy.

Criteria for discharge were prespecified: 1) passage of stools, 2) The patient tolerates per oral nutrition, 3) sufficient pain relieve was achieved with ibuprofen, paracetamol, and/or tramadol.

Outcomes

Primary outcome of the trial was postoperative length of hospital stay assessed at time of discharge. Secondary outcomes were time to passage of stools during hospital stay, time to commencement of enteral nutrition during hospital stay, 30-day mortality, complications graded by Clavien-Dindo classification within 30 days, number of participants with iatrogenic small bowel lesions detected at the operation or within hospital stay, number of participants with readmissions within 30 days, number of participants with failure to resolve obstruction during hospital stay, pain score on visual analog scale in the first seven postoperative days, length of epidural catheter analgesia during hospital stay, total need of opiods during hospital stay, length of sick leave assessed at 30-day follow-up or at the end of sick leave, and conversion rate assessed during operation. Opioids were converted morphine equivalent doses using conversion factors of

0·1 for tramadol and 1·5 for oxycodone. Pain was evaluated using Visual Analog Scale daily, and always before administrating pain killers. Length of sick leave was registered in patients who were discharged to home, under 65 years, and not pensioned. The length of sick leave was at the discretion of surgeon, who took into consideration patient's age and type of work. Thirty-day follow-up was undertaken by a phone call to the patient, and return to work, possible late complications, and readmissions were registered. The reported sick leave was based on the actual date on which the patient returned to work. The data was gathered prospectively using an electronical (Finnish hospitals) or paper case report forms (Italian hospitals).

Statistical analysis

Based on data derived from earlier retrospective series,[17] we aimed to show that the laparoscopic approach would shorten the postoperative length of stay by 2·5 days, and estimated the mean postoperative length of stay in open group to be 7·25 days (SD 5) and 4·75 days (SD 3·75) in laparoscopic group. Sample size calculation was based on two-sided t-test for two independent means. We calculated that 102 patients are needed to show this difference with 80% power at 5% significance level.

Continuous outcomes with non-normal distrubution were log-transformed (natural logarithm) to obtain normal distribution, and log-transformed outcomes were then compared using t-test. Obtained means were then back transformed using anti-log function to obtain geometric means. Effect size for such outcomes were reported as ratio of geometric means and its 95% confidence interval. Variables that had non-normal distribution and could not be log-transformed into normal distribution, were compared using Mann-Whitney-U-test. Effect size for such outcomes was reported as r (=Z/√N) without 95% confidence intervals. Categorical outcomes were compared using Fischer's exact-test (if expected cases in one cell < 5) or Chi-square-test. Effect size for

categorical outcomes were reported as odds ratio with 95% confidence intervals. Statistical analyses were performed using SPSS Statistics 24 software (IBM, Armonk, NY). Statistical significance was set at a two-sided alpha level of 0·05, without correction for multiple testing. Number of cases with missing data is stated either in the manuscript text or tables. Cases with missing data were omitted from analyses of that specific variable of interest. All outcomes were analyzed using modified intention-to-treat principle, which included all the patients who were randomised according to the trial protocol's inclusion and exclusion criteria, and proceeded to surgery (i.e. the obstruction did not resolve while waiting for surgery). There was one change in the study protocol in May 2014 : the inclusion criteria originally stated "48-hour conservative treatment without Gastrografin is allowed for iodine allergic patients", and was changed to "48-hour conservative treatment without Gastrografin is allowed if Gastrografin is contraindicated (e.g. allergy) or not available". No other changes to the study protocol was made after the commencement of the trial.

Role of the funding source

The funding sources did not have any role, in study design, in the collection, analysis, interpretation of data, in the writing of the report, or in the decision to submit the paper for publication. VS and PM had access to the raw data of all patients. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Patients

One hundred and four patients were enrolled in eight hospitals in Finland and Italy between 18th July 2013 and 9th April 2018 (see Appendix p1). The study was ended because calculated sample size was achieved. Details of assessment, exclusion and allocation are shown in Figure 1. One hundred patients were included in the modified intention-to-treat analyses. Two patients were excluded because the obstruction resolved before surgery, and two patients were excluded because they were randomised in spite of exclusion criteria met (Figure 1). The open and laparoscopic adhesiolysis groups were highly similar in regard to age, sex, body-mass-index, ASA score, comorbidities, duration of symptoms, earlier ileus, earlier abdominal operations, nasogastric tube secretion prior surgery (Table 1). Despite rigorous selection of patients with aim of a single adhesive band causing obstruction, approximately one third in both groups had more adhesions than a single band (Table 1). Five patients in the open surgery group had non-adhesive ileus.

Treatment

97 patients received Gastrografin challenge, while two patients were not administered Gastrografin® owing to having conservative therapy over 48 hours and one patient was not administered Gastrografin due to allergy. Patients were operated by 23 surgeons. Duration of surgery was 46 minutes (interquartile range [IQR], 31 to 70) in open group and 50 minutes (IQR, 34 to 70) in laparoscopy group. The total length of operative room stay was 124 minutes (IQR 109 to 150) in open group and 120 minutes (IQR 105 to 139) in laparoscopy group. Bowel resection was performed in 12 patients (24%) in open group and in 2 patients (4%) in laparoscopy group. The reasons for bowel resection in open surgery group were irreversible ischemia in six, incidental Meckel's diverticulum in one, adhesive stricture in one, inflammatory stricture in one, cancer in two, and full thickness iatrogenic bowel perforation in one patient. The reasons for bowel

resection in laparoscopic group were bowel perforation (non-iatrogenic) in one and irreversible ischemia in one patient. Surgery in 13 patients (25%) in laparoscopic group were converted to open surgery at median 20 minutes (IQR 10 to 40) from the beginning of the surgery. All conversions to open surgery were performed through midline incision. The reason for conversion was following: unable to find obsructive adhesion in 3 patients, unable to relieve obstructive adhesion in one patient, diffuse adhesions in 3 patients, iatrogenic bowel lesion in 3 patients, need for bowel resection in 2 patients, and bowel perforation (not iatrogenic) in one patient. Median length of laparotomy incision was 12 cm (IQR, 11 to 17, data missing in one patient) in open group, and 20 cm (IQR, 13 to 20) in 13 patients in laparoscopy-converted-to-open-surgery group.

Outcomes

The postoperative length of stay for open group was on average 1·3 days longer than that in laparoscopy group (geometric mean 5·5 (range 2 – 19) versus 4·2 (range 1 - 20), ratio of geometric means 1·31 (95% confidence interval 1·06 – 1·61), p = 0·013). The total length of hospital stay stay for open group was on average 1·5 days longer than that in laparoscopy group (geometric mean 8·5 (range 5 – 21) versus 7·0 (range 3 - 24), ratio of geometric means 1·21 (95% confidence interval 1·05 – 1·41), p = 0·009).

Time from surgery to bowel function was shorter in laparoscopy group (geometric mean 41 hours) than in open group (geometric mean 63 hours), but median time to per oral feeding was similar between the groups (geometric means 30 hours in laparoscopy group, 35 hours in open group) (Table 2). Parenteral nutrition was given in 7 patients (14%) in both groups. Median nasogastric tube secretion after surgery was 300 ml [IQR, 100 to 855] in open and 380 ml [IQR, 100 to 800] laparoscopic group. Obstruction was relieved by first surgery in all patients. One

patient in the open group was readmitted due to urinary tract infection and relative ileus. Three patients were readmitted in the laparoscopy group due to colitis, ileus, and pneumonia.

The rate of complications (21 (43%) vs. 16 (31%), p = 0·23, odds ratio [OR] 0·61 (95% CI 0·27 – 1·38)), clinically significant complications (Clavien-Dindo grade 2 or higher, 12 (24%) vs. 8 (16%), p = 0·27, OR 0·57 (0·21 – 1·55)), or in major complications (Clavien-Dindo 3 or higher, 3 (6%) vs. 4 (8%), p = 0·74, OR 1·31 (0·28 – 6·16)) was similar between open and laparoscopic groups, respectively (Table 3). Surgical site infections were detected in 3 patients (6%) in open group and in 3 patients (6%) in laparoscopy group (Table 3). The rate of iatrogenic bowel lesions was similar between the groups (Table 2). There were 9 serosal tears and 2 full thickness iatrogenic perforations in open group and 8 serosal tears and 4 full thickness iatrogenic perforations in laparoscopy group. Only one bowel perforation was unnoticed during primary surgery (in laparoscopy group), and this led to peritonitis, and ultimately death of the patient (see next paragraph).

One patient died within 30 days from randomisation in both open and laparoscopy groups. An elder and comorbid patient in the open group did not give consent to operatively relieve small bowel obstruction until five days of conservative therapy including Gastrografin challenge was not relieving the obstruction. When consent was obtained, the patient was enrolled and operated. One adhesive band was released in surgery and no iatrogenic bowel lesion occurred. The patient deterioated quickly after surgery and died of multi-organ failure during 1. postoperative day in intensive care unit. Another elder and comorbid patient in the laparoscopic group underwent laparoscopic adhesiolysis without conversion for local diffuse adhesions (not a single band). No bowel lesion was noticed during primary operation. The patient was reoperated for clinical peritonitis on third postoperative day via midline laparotomy. A small bowel perforation was sutured in the area of adhesiolysis. The patient also had a pneumonia, which was diagnosed prior

primary operation. The patient met the prespecified discharge criteria, the overall status was improving, the patient was discharged to rehabilitation hospital on 11th postoperative day. The patient was readmitted on 14th postoperative day in shock and died in the emergency room. Autopsy concluded that the patient died of coronary heart disease, and that the postoperative peritonitis had settled, but was a factor in the death along with pneumonia.

Pain on visual analog scale was lower in laparoscopy group than open group on postoperative days 3 and 4 (Figure 2). Epidural catheter was inserted in 28 patients (57%) in open group and in 5 patients (10%) in laparoscopy group ($p < 0{\cdot}0001$). Wound analgesia catheters were inserted in 3 patients (6%) in open group and in 2 patients (4%) in laparoscopy group. The length of epidural catheter was longer in open group (median 39 hours versus median 0 hours) (Table 2). Opioid use was similar in both groups (Table 2).

The length of sick leave was on average 12 days longer in open group than in laparoscopy group (geometric means 24 days versus 12 days) (Table 2).

Discussion

In this international, multicenter trial, we randomised patients with acute small bowel obstruction resistant to non-operative treatment to undergo either open or laparoscopic adhesiolysis. Patients randomised to laparoscopic approach had shorter length of hospital stay, quicker return of bowel function, less inserted epidural catheters, less postoperative pain, and shorter sick leave. There were no differences in complications, bowel injury, or opioid use.

Several earlier systematic reviews and meta-analyses of non-randomised series have found dramatic drop in morbidity, mortality, wound infections, and length of stay.[7-10] As there is no other randomised trial, this study provides the best evidence so far for the differences between open and laparoscopic approach for small bowel obstruction. Contrary to earlier non-randomised series,

our study did not find differences in morbidity, mortality, or wound infections. Length of stay was shortened by approximately one day in current trial, while earlier series have reported typically 3- to 4-day difference in favor of laparoscopy even in adjusted analyses.[12,18 13,17,19-21] It seems clear, and also acknowledged before, that less severe cases were selected for laparoscopic approach in the earlier series,[10,11] and this bias cannot be abolished by statistical means. Along with shorter hospital stay, we found quicker return of bowel function (71 hours versus 43 hours) and reduced use of epidural catheter (57% vs 10%) in the laparoscopy group. While return of bowel function might be of less clinical value, insertion of epidural catheter is an invasive procedure with a risk of epidural haematoma around 1:3500.[22] One of the feared complication of laparoscopic adhesiolysis is iatrogenic bowel injury. A recent publication from Canada reporting over 8000 patients undergoing operation for adhesive small bowel obstruction reported increased risk of bowel injury in patients undergoing laparoscopic approach compared to open approach (odds ratio 1.6).[12] Some series have reported bowel injury in 6·3 to 26·9% of patients undergoing laparoscopy adhesiolysis for small bowel obstruction.[17,23-25] The figure in this trial (22%) is comparable to these figures, but the rate of bowel injury was similar in open group (22%) also. A possible reason for lower rate of iatrogenic bowel injury in earlier non-randomised studies is reporting bias i.e. small lesions might not be accurately collected in retrospective data collection. However, unnoticed iatrogenic bowel injury present a potential for severe complications, and this occurred in one patient with diffuse adhesions in the laparoscopy group, who later died of cardiovascular complications after having had a reoperation for peritonitis. We therefore suggest low threshold for conversion to open surgery in cases where the obstruction is not caused by a single band.

Our trial has several limitations. First, the sample size was relatively small and some analyses might suffer from type 2 error (aka false negative results). Although small bowel obstruction is relatively common emergency, large proportion is resolved without surgery, and

only a portion of the ones needing surgery are suitable for laparoscopic approach. Further, laparoscopic adhesiolysis is a demanding procedure, and needed expertise is not always present during off-duty hours, especially in lower volume hospitals.[3] Further, randomised clinical trials are notoriously difficult to carry out in emergency surgery. Current trial enrolled patients in eight hospitals in two countries, and it took five years to recruit the target sample size. It is unlikely that a larger randomised trial comparing laparoscopy to open surgery for adhesive small bowel obstruction will be executed. Second, this trial had strict inclusion and exclusion criteria in order to select patients with high likelihood of a single adhesive band causing the obstruction. This is reflected by the fact that nearly 600 patients were screened in order to enroll hundred patients. Thus the results of the trial are not representative to all patients with adhesive small bowel obstruction. However, even in this highly selected population conversion to open surgery occurred in 25%, and iatrogenic bowel injury in 22% of the patients. It is likely that these figures would be higher had more complex cases been included. On the other hand, our results are highly externally valid as the trial was commenced in two countries' eight hospital, of which three were not acadamedic university hospitals, and large pool of surgeons were operating on the patients. However, we did not account for surgeons or centers in the analyses of the outcomes. Additionally, we had prespecified criteria for discharge, but the protocol did not outline specific indications for commencement and cessation of parenteral nutrition. Finally, we report only short-term results, and laparoscopic approach might have additional benefits in the long-term. Our plan is to continue follow-up up to 10 years from randomisation, and next report is scheduled to be released after 5-year follow-up has been achieved in all patients. These long-term outcomes will include rates of incisional hernias and recurrent small bowel obstruction, which are hypothesized to be lower in laparoscopy group. On the other hand, a retrospective series reported increased incidence of recurrent small bowel obstruction associated with laparoscopic adhesiolysis.[26]

In conclusion, our results indicate that laparoscopic adhesiolysis in small bowel obstruction results in quicker recovery. The criteria introduced in this trial may be used as a guideline to select patients for laparoscopic approach.

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Author contribution

Original concept: VS, AL, PM

Design of the study protocol: VS, EH, HW, VK, AL, PM

Data collection: VS, SDS, EH, RJ, HW, VK, FC, BE, AB, PM

Data analysis: VS, PM

Initial draft: VS

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Figure legends

Figure 1. Enrollment, randomisation, and follow-up.

Figure 2. Pain during hospital admission. Pain was lower in laparoscopy group on day 3 (median 2 (IQR 1 – 3) versus median 1 (IQR 0 – 2), p = 0·006, r = 0·32) and day 4 (median 1·5 (IQR 0·5 – 3) versus 0·5 (IQR 0 – 1·5), p = 0·015, r = 0·32) compared to open group, respectively.

References

1. Scott JW, Olufajo OA, Brat GA, et al. Use of National Burden to Define Operative Emergency General Surgery. JAMA Surg 2016;151(6):e160480.

2. Broek ten RPG, Issa Y, van Santbrink EJP, et al. Burden of adhesions in abdominal and pelvic surgery: systematic review and met-analysis. BMJ 2013;347(oct03 1):f5588–8.

3. Di Saverio S, Birindelli A, Broek Ten R, Davies JR, Mandrioli M, Sallinen V. Laparoscopic adhesiolysis: not for all patients, not for all surgeons, not in all centres. Updates in Surgery 2018;266(3):1–5.

4. Kauppila JH, Xie S, Johar A, Markar SR, Lagergren P. Meta-analysis of health-related quality of life after minimally invasive versusopen oesophagectomy for oesophageal cancer. Br J Surg 2017;104(9):1131–40.

5. Palanivelu C, Senthilnathan P, Sabnis SC, et al. Randomized clinical trial of laparoscopic versusopen pancreatoduodenectomy for periampullary tumours. Br J Surg 2017;104(11):1443–50.

6. Hong SK, Lee KW, Choi Y, et al. Initial experience with purely laparoscopic living-donor right hepatectomy. Br J Surg 2018;105(6):751–9.

7. Sajid MS, Khawaja AH, Sains P, Singh KK, Baig MK. A systematic review comparing laparoscopic vs open adhesiolysis in patients with adhesional small bowel obstruction. Am J Surg 2016;212(1):138–50.

8. Wiggins T, Markar SR, Harris A. Laparoscopic adhesiolysis for acute small bowel obstruction: systematic review and pooled analysis. Surg Endosc 2015;29(12):3432–42.

9. Li M-Z, Lian L, Xiao L-B, Wu W-H, He Y-L, Song X-M. Laparoscopic versus open adhesiolysis in patients with adhesive small bowel obstruction: a systematic review and meta-analysis. Am J Surg 2012;204(5):779–86.

10. Cirocchi R, Abraha I, Farinella E, Montedori A, Sciannameo F. Laparoscopic versus open surgery in small bowel obstruction. Cochrane Database Syst Rev 2010;21(2):CD007511.

11. Broek ten RPG, Krielen P, Di Saverio S, et al. Bologna guidelines for diagnosis and management of adhesive small bowel obstruction (ASBO): 2017 update of the evidence-based guidelines from the world society of emergency surgery ASBO working group. World Journal of Emergency Surgery 2018;13(1):1–13.

12. Behman R, Nathens AB, Byrne JP, Mason S, Look Hong N, Karanicolas PJ. Laparoscopic Surgery for Adhesive Small Bowel Obstruction Is Associated With a Higher Risk of Bowel Injury: A Population-based Analysis of 8584 Patients. Ann Surg 2017;266(3):489–98.

13. Pei KY, Asuzu D, Davis KA. Will laparoscopic lysis of adhesions become the standard of care? Evaluating trends and outcomes in laparoscopic management of small-bowel obstruction using the American College of Surgeons National Surgical Quality Improvement Project Database. Surg Endosc 2016;31(5):2180–6.

14. Lee MJ, Sayers AE, Wilson TR, et al. Current management of small bowel obstruction in the UK: results from the National Audit of Small Bowel Obstruction clinical practice survey. Colorectal Disease 2018;20(7):623–30.

15. Di Saverio S, Coccolini F, Galati M, et al. Bologna guidelines for diagnosis and management of adhesive small bowel obstruction (ASBO): 2013 update of the evidence-based guidelines from the world society of emergency surgery ASBO working group. World Journal of Emergency Surgery 2013;8(1):1–1.

16. Sallinen V, Wikström H, Victorzon M, et al. Laparoscopic versus open adhesiolysis for small bowel obstruction - a multicenter, prospective, randomized, controlled trial. BMC Surg 2014;14(1):77.

17. Hackenberg T, Mentula P, Leppäniemi A, Sallinen V. Laparoscopic versus Open Surgery for Acute Adhesive Small-Bowel Obstruction: A Propensity Score-Matched Analysis. Scand J Surg 2016;

18. Patel R, Borad NP, Merchant AM. Comparison of outcomes following laparoscopic and open treatment of emergent small bowel obstruction: an 11-year analysis of ACS NSQIP. Surg Endosc 2018;210(12):201–12.

19. Byrne J, Saleh F, Ambrosini L, Quereshy F, Jackson TD, Okrainec A. Laparoscopic versus open surgical management of adhesive small bowel obstruction: a comparison of outcomes. Surg Endosc 2014;:1–8.

20. Saleh F, Ambrosini L, Jackson T, Okrainec A. Laparoscopic versus open surgical management of small bowel obstruction: an analysis of short-term outcomes. Surg Endosc 2014;28(8):2381–6.

21. Davies SW, Gillen JR, Guidry CA, et al. A Comparative Analysis between Laparoscopic and Open Adhesiolysis at a Tertiary Care Center. Am Surg 2014;80(3):261–9.

22. Landoni G, Isella F, Greco M, Zangrillo A, Royse CF. Benefits and risks of epidural analgesia in cardiac surgery. Br J Anaesth 2015;115(1):25–32.

23. Johnson KN, Chapital AB, Harold KL, Merritt MV, Johnson DJ. Laparoscopic management of acute small bowel obstruction. Journal of Trauma and Acute Care Surgery 2012;72(1):25–31.

24. Grafen FC, Neuhaus V, Schöb O, Turina M. Management of acute small bowel obstruction from intestinal adhesions: indications for laparoscopic surgery in a community teaching hospital. Langenbecks Arch Surg 2009;395(1):57–63.

25. Wullstein C, Gross E. Laparoscopic compared with conventional treatment of acute adhesive small bowel obstruction. Br J Surg 2003;90(9):1147–51.

26. Yao S, Tanaka E, Matsui Y, et al. Does laparoscopic adhesiolysis decrease the risk of recurrent symptoms in small bowel obstruction? A propensity score-matched analysis. Surg Endosc 2017;31(12):5348–55.

Table 1. Demographic and operative characteristics of included patients

	Open surgery (N = 49)	**Laparoscopy (N = 51)**
Median age (IQR, range) - yr	74 (60 – 84, 24 - 94)	73 (60 – 81, 32 - 93)
Female sex - no. (%)	31 (63%)	34 (67%)
Mean Body Mass Index (SD) - kg/m^2	23.2 (3.8)	24.8 (4.7)
ASA physical status - no. (%)		
1	5 (10%)	2 (4%)
2	12 (25%)	16 (31%)
3	20 (41%)	23 (45%)
4	12 (25%)	10 (20%)

	Open surgery (N = 49)	Laparoscopy (N = 51)
Comorbidities - no. (%)		
Myocardial infarction	4 (8%)	4 (8%)
Congestitve heart failure	4 (8%)	1 (2%)
Coronary disease (not infarction)	8 (16%)	2 (4%)
Hypertension	17 (35%)	22 (43%)
Peripheral vascular disease	1 (2%)	2 (4%)
Cerebrovascular disease	2 (4%)	4 (8%)
Hemiplegia	0	0
Dementia	0	1 (2%)
COPD	5 (10%)	9 (18%)
Connective tissue disease	0	1 (2%)
Liver disease		
Mild	0	2 (4%)
Moderate / Severe	0	0
Peptic ulcer disease	3 (6%)	0
Diabetes mellitus		
without complications	5 (10%)	4 (8%)
with complications	1 (2%)	0
Kidney disease (moderate / severe)	2 (4%)	0
Solid tumor	2 (4%)	1 (2%)
Metastatic malignancy	1 (2%)	2 (4%)
Leukemia	0	0
Lymphoma	1 (2%)	0
AIDS	0	0
No comorbidities	12 (25%)	12 (24%)

	Open surgery (N = 49)	Laparoscopy (N = 51)
Median duration of symptoms prior admission (IQR) - hours	46 (13 - 72)	48 (23 - 120)
Number of previous conservatively managed ileus - no. (%)#		
0	42 (89%)	46 (90%)
1	4 (9%)	5 (10%)
2	1 (2%)	0
Number of earlier abdominal operations - no. (%)##		
0	4 (8%)	6 (12%)
1	27 (55%)	22 (43%)
2	15 (31%)	21 (41%)
3	3 (6%)	2 (4%)
Median nasogastric tube secretion before surgery (IQR) - ml	2800 (1000 - 4600)	2700 (1300 - 3781)###
Cause of obstruction detected at surgery - no. (%)		
Single adhesive band	27 (55%)	30 (59%)
Adhesions, more than one band	13 (27%)	17 (33%)
Peritoneal pouch / internal hernia	2 (4%)	4 (8%)
Scarring of bowel wall, no band	2 (4%)	0
Intraluminal fecolith	2 (4%)	0
Paralysis, no obstruction	1 (2%)	0
Cancer	2 (4%)	0

	Open surgery (N = 49)	Laparoscopy (N = 51)
Bowel status as detected at surgery - no. (%)		
Vital	36 (74%)	36 (71%)
Reversible ischemia	7 (14%)	12 (24%)
Irreversible ischemia / necrosis / perforation	6 (12%)	3 (6%)€

AIDS = acquired immunodeficience syndrome. ASA = The American Society of Anesthesiologists (ASA) physical status classification systems. COPD = chronic obstructive pulmonary disease. IQR = interquartile range. No significant differences were identified between the treatment groups in any baseline variables, except for “Coronary disease (not infarction)” p = 0.049.

#data missing from 2 patients in open surgery group.

##Includes also ceasarean sections and laparoscopic procedures. None of the patients had 3 (or more) open abdominal operations in history (which would have been exclusion criteria).

###data missing in one patient

€small point necrosis perforation in two patients

Table 2. Primary and secondary outcomes

	Open surgery (N = 49)	Laparoscopy (N = 51)	P value	Effect size (95% CI)&&&
Primary outcome				
Mean&& length of postoperative hospital stay (range) - days	5·5 (2 – 19)†	4·2 (1 – 20)	0·013	1·31 (1·06 – 1·61)
Secondary outcomes				
Mean&& time to bowel function (range) - hours	63 (5 - 268)#	41 (3 - 175)‡	0·007	1·54 (1·11 – 2·11)
Mean&& time to per oral feeding (range) - hours	35 (13 - 255)#	30 (7 - 163)‡	0·23	1·18 (0·90 – 1·54)
Death at 30 days - no. (%)	1 (2%)	1 (2%)	1	0·96 (0·06 – 15·8)
Iatrogenic bowel lesions - no. (%)	11 (22%)	12 (24%)	0·90	1·06 (0·42 – 2·70)

	Open surgery (N = 49)	Laparoscopy (N = 51)	P value	Effect size (95% CI)&&&
Readmission within 30 days, n (%)	1 (2%)†	3 (6%)	0·62	2·94 (0·30 – 29·26)
Median length of epidural catheter (IQR), hours	39 (0 - 54)	0 (0 - 0)	<0·0001	0·51
Median opioid / day (IQR) ## - mg of morphine equivalent€€	5.7 (1.0 - 12.0)	3.6 (0 - 12.2)	0·47	0·07
Mean&& length of sick leave (range) - days###	24 (12 - 65) n = 10	12 (3 - 49) n = 11	0·04	1·90 (1·03 – 3·51)

IQR = interquartile range. SD = standard deviation.

&&geometric mean

&&&For geometric means, ratio of geometric means is given with 95% confidence interval. For means, difference of means is given with 95% confidence interval. For binary outcomes, odds ratio is given with 95% confidence interval. For medians, r = Z/√N is given withouth 95% confidence intervals.

†available for 48 patients as one patient died during primary hospital stay

‡missing in 1 patient

#missing in 2 patients

##per postoperative day during hospital stay, missing in 2 patients in open surgery arm

€€Calculated from tramadol and oxycodone usage

###valid for patients discharged to home, age below 65 years, and not pensioned.

Table 3. Postoperative complications within 30 days

	Open surgery (n = 49)	Laparosopy (n = 51)
Clavien-Dindo grade and type - no. (%)		
None	***28 (57%)***	***35 (69%)***
1	***9 (18%)***	***8 (16%)***
Superficial wound infection	1 (2%)	0
Electrolyte inbalance	4 (8%)	5 (10%)
Urinary retention	1 (2%)	0
Diarrhea	0	1 (2%)
Diuretics	3 (6%)	1 (2%)
Incision site bleeding	0	1 (2%)
2	***9 (18%)***	***4 (8%)***
Prolonged ileus with Gastrografin	1 (2%)	0
Prolonged ileus with parenteral nutrition	2 (4%)	2 (4%)
Fever with antibiotics	2 (4%)	0
Pneumonia	1 (2%)	1 (2%)
Urinary tract infection	2 (4%)	0
Postoperative delirium	1 (2%)	0
Colitis	0	1 (2%)
3a	***1 (2%)***	***2 (4%)***
Pleural drainage	1 (2%)	1 (2%)
Intra-abdominal abscess with drainage	0	1 (2%)

	Open surgery (n = 49)	Laparosopy (n = 51)
3b	***1 (2%)***	***0***
Fascial rupture and resuturation	1 (2%)	0
4a	***0***	***0***
4b	***0***	***1 (2%)***
Pneumonia leading to intensive care	0	1 (2%)
5 (death)	***1 (2%)***	***1 (2%)***
Multi-organ failure	1 (2%)	0
Cardiac failure, sequlae of bowel injury	0	1 (2%)
Surgical site infections - no. (%)		
Any	3 (6%)	3 (6%)
Superficial incisional	2 (4%)	1 (2%)
Deep incisional	1 (2%)	0
Organ / space	0	2 (4%)

Data sharing statement: The collected data or related documents will not be made available to others.

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566 Patients were assessed for eligibility

462 Were excluded

- 180 Did not meet inclusion criteria (48 had no small bowel occlusion in CT, 132 occlusion resolved with conservative means)
- 239 Had exclusion criteria (some patients had several exclusion criteria)
  - Suspicion of strangulation or peritonitis (n=49)
  - Confirmed/suspected peritoneal carcinosis (n=14)
  - Known wide adhesions (n=27)
  - Previous open surgery for endometriosis (n=9)
  - Previous generalized peritonitis (n=16)
  - Abdominal malignancy (or remission < 10 years) (n=56)
  - Previous radiotherapy of the abdominal region (n=25)
  - Previous obesity surgery (n=2)
  - 3 or more earlier open abdominal operations (n=64)
  - Suspicion of other source of obstruction than adhesions (n=25)
  - Recent abdominal operation (within 30 days) (n=23)
  - Previous laparotomy for aorta or iliac vessels (n=7)
  - Crohn's disease (n=2)
  - Anesthesiological contraindication for laparoscopy (n=6)
  - Patient living in institutionalized care (n=14)
  - Hospital stay more than one week prior to surgical consultation (n=21)
  - Age > 95 years (n=1)
- 18 Declined to participate
- 25 Had other reason
  - Patient transferred to another hospital for treatment (n=2)
  - On-call surgeon not experienced in laparoscopic adhesiolysis (n=14)
  - Patient not living in Finland, follow-up impossible (n=1)
  - Unable to obtain written consent due not speaking Finnish or Swedish (n=1)
  - Mentally disabled (n=1)
  - Dementia (n=2)
  - On-call surgeon decided to operate (n=3)
  - Treatment restricted to non-operative means due to terminal malignancy (n=1)

104 Patients underwent randomization

51 Were allocated to open surgery

50 Received allocated intervention

1 Did not receive allocated intervention owing to resolving obstruction before planned surgery

53 Were allocated to laparoscopy

52 Received allocated intervention

1 Did not receive allocated intervention owing to resolving obstruction before planned surgery

1 was excluded the analysis owing to not receiving intervention (outcomes not accessible)

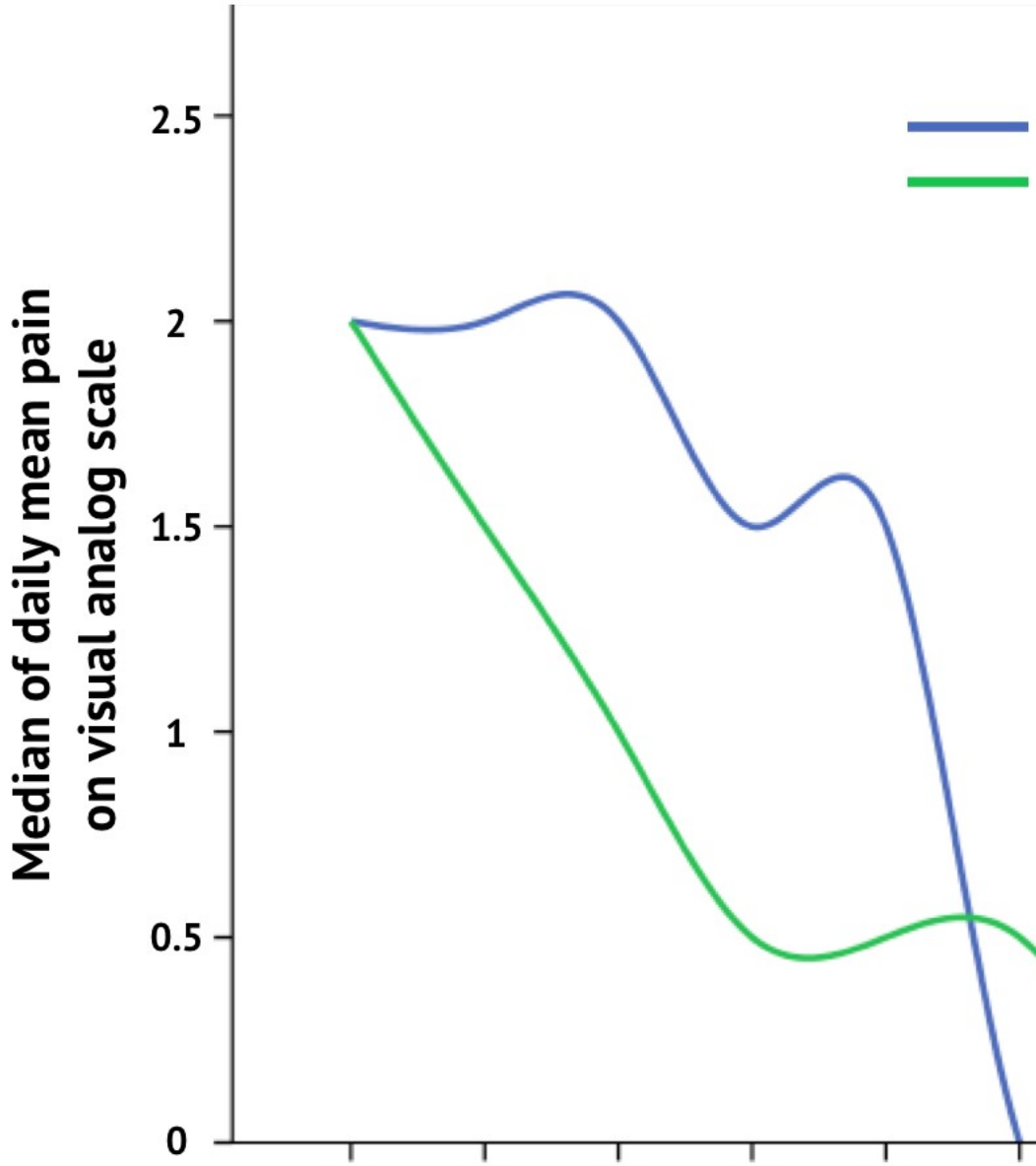
1 was excluded owing to severe protocol violation (randomized in spite of exclusion criteria met (earlier abdominal malignancy and radiotherapy)

1 was excluded the analysis owing to not receiving intervention (outcomes not accessible)

1 was excluded owing to severe protocol violation (randomized in spite of exclusion criteria met (earlier abdominal malignancy)

49 Were included in the modified intention-to-treat analysis

51 Were included in the modified intention-to-treat analysis



Patients alive at hospital	99	97	86	72	52	43
Patients with missing data	7	8	11	12	9	9