Title

No benefit of ultrasound guided transversus abdominis plane (TAP) blocks over local anaesthetic wound infiltration in elective laparoscopic colonic surgery; results of a double blind randomised controlled trial.

Short title

TAP block for laparoscopic colonic resection

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ABSTRACT

AIM: Advances in laparoscopic techniques combined with enhanced recovery pathways have led to faster recuperation and discharge after colorectal surgery. Peripheral nerve blockade using Transversus Abdominis Plane (TAP) blocks reduce opioid requirements and provide better analgesia than inactive controls for laparoscopic colectomies. This double-blind randomized study was performed comparing TAP blocks **using Bupivacaine** to standardised wound infiltration with local anaesthetic (LA).

METHODS: 71 Patients were randomised between either TAP-block or wound infiltration. The TAP blocks were performed by experienced anaesthetists who used ultrasound guidance to deliver 40ml of 0.25% **Bupivacaine post-induction** in the transverse abdominis plane. In the control group 40ml of 0.25% **Bupivacaine** was injected around the trocar- and extraction site by the surgeon. Both groups received patient controlled analgesia (PCA) with intravenous morphine. Patients and nursing staff assessed pain scores at 6, 12, 24 and 48 hours after surgery. Primary outcome was overall morphine use in the first 48 hours.

RESULTS: Of the 71 patients 20 underwent a right hemi-colectomy and 51 a high anterior resection. The modified intention-to-treat analysis showed no significant differences in overall morphine use {47.3 (36.2–58.5) vs 46.7 (36.2–57.3) mg, Mean (95% CI) p =0.8663) in the first 48 hours. Pain scores were similar at 6, 12, 24 & 48hours. No differences were found regarding time to mobilisation, resumption of diet and length of hospital stay.

CONCLUSION: **In elective laparoscopic colectomies standardised wound infiltration with LA has the same analgesic effect as TAP blocks post-induction using Bupivacaine at 48 hours.**

WHAT DOES THIS PAPER ADD TO THE LITERATURE?

In patients undergoing elective laparoscopic colonic resections, LA infiltration of port and extraction sites at the end of surgery is equivalent to bilateral ultrasound-guided TAP blocks **post-induction using Bupivacaine** performed on induction using the same concentration and volume of LA, in terms of total morphine consumption, pain control and recovery.

INTRODUCTION

The advances in laparoscopic techniques combined with enhanced recovery pathways have led to faster recuperation and discharge after colorectal surgery. Effective postoperative pain relief is essential to facilitate improved surgical outcomes.[1, 2.] Multimodal analgesia is the gold standard. ~~However analgesic strategies including neuraxial blocks, intravenous opioids and non-steroidal anti-inflammatory drugs can have side effects that interfere with rapid recovery and/or wound healing.[3]~~ Pain from surgical trauma to the anterior abdominal wall, which is a significant component of pain after laparoscopic colectomies, could be reduced by LA wound infiltration or peripheral nerve blocks (PNB).[3]

First described by Rafi in 2001,[4] TAP blocks have recently gained popularity. In this technique, LA is injected in the neurovascular plane between the transversus abdominis and the internal oblique muscle blocking the anterior rami of the lower 6 thoracic nerves (T7-T12) and the first lumbar (L1) nerve, thereby reducing pain sensation from the anterior abdominal wall.[4,5]

The evidence for TAP blocks in laparoscopic colorectal surgery is limited to observational data[6-9] and two randomized controlled trials.[10,11] These trials demonstrated significantly reduced opioid use in the TAP group compared to controls in the first 24hours after surgery. These studies, together with several meta-analyses including a Cochrane review[12, 13] have solely focused on the comparison of TAP vs inactive control or placebo.

This is the first study to compare TAP blocks utilizing Bupivacaine to LA wound infiltration. This study was designed to compare the effect of TAP blocks to LA wound infiltration in the 48h after elective laparoscopic colectomy.

METHODS

This study was registered with an international registry, clinical-trials.gov (identification number NCT01339273) before patient recruitment. The national research ethics service (NRES) committee South Central – Oxford- A, United Kingdom (Reference number 11/SC0205) approved the study. Informed written consent was obtained from all participants.

This single-centre, randomized trial recruited patients from a tertiary teaching hospital, Oxford University Hospitals, between October 2011 and November 2013. Eligible patients were aged 18 or above, able to provide written consent, of ASA physical status 1-3 and had colorectal disease (benign or malignant) suitable for elective laparoscopic right hemicolectomy or high anterior resection without stoma formation.

Patients were not studied if there was a history of chronic abdominal pain, opioid tolerance, allergy or intolerance to either Morphine or LAs, BMI>35 Kg/M2, **high likelihood of conversion to open procedure due to previous major abdominal surgery,** patients unable to communicate in written and spoken English or weight less than 50 kg.

Randomisation and blinding

On the day of surgery, consenting patients were randomly assigned to receive either TAP block or LA (1:1) using a random allocation sequence concealed in 72 consecutively numbered, sealed opaque envelopes. All patients, nursing staff and treating physicians doing follow-up were fully blinded to the method of analgesia until the study was completed. The surgeons and anaesthetists present in theatre were not blinded and were not involved in study follow up.

Anaesthesia, surgery and postoperative analgesia

Standard procedures for surgery, anaesthesia and analgesia were followed. After securing intravenous access, pre-oxygenation and routine monitoring according to AAGBI standards, general anaesthesia

was induced with Propofol 2-3 mg/kg and Fentanyl 1.5 mcg/kg (Max 100 mg). Postoperative nausea and vomiting (PONV) prophylaxis was given as per hospital guidelines. Tracheal intubation was performed after administration of muscle relaxants and anaesthesia maintained with 1 MAC isoflurane in oxygen and air mixture with intermittent positive pressure ventilation. All patients received morphine 0.15mg/kg body weight in titrated doses during the procedure and 1g IV paracetamol 30 minutes before completion of the procedure.

All surgery was performed or supervised by 3 consultant colorectal surgeons. After open introduction of a 12 mm umbilical trocar, a pneumoperitoneum of 12mm Hg CO2 was created and additional 5mm trocars placed. Colectomies were performed according to standard oncological principles. The extraction site of the specimen was the umbilicus for all right-sided hemicolectomies. For the high anterior resections the site of extraction was either a left-inferior-quadrant incision or Pfannenstiel supra-pubic incision. Extraction site, size of fascial and skin incision, number of trocars, operative time and possible adverse events were recorded by the surgeon.

TAP blocks were performed immediately following induction of anaesthesia by 3 anaesthetists experienced in performing TAP blocks. Real time ultrasound guidance (Sonosite^{TM}, Bothell, WA, USA) was used to deliver 20 mls of 0.25% bupivacaine per side in an in-plane approach using a 100mm Stimuplex needle (Braun, Melsungen, Germany). The block was placed anterolateral in the sheet at the mid-axillary line. Confirmation of position of the block was by visualisation of separation of the middle and inner layers with expansion of injected volume. **The procedures were recorded for independently review and assessment of correct placement of the block. ~~TAP block cases were analysed regardless of whether blocks were recorded or not.~~** In the control group 40ml of 0.25% Bupivacaine was injected pre-peritoneally and sub-fascially at the extraction and trocar sites by the surgeon at the end of the procedure.

A standardised postoperative analgesic regimen, consisting of regular paracetamol 1 gram every 6 hours, and PCA rescue with intravenous morphine was instituted. PCA was started at 1 mg bolus with

5 minute lockout without background infusion. Oral step down was introduced as deemed appropriate by our acute pain team. Total opioid consumption was recorded and then converted to standard morphine equivalents. NSAIDs were not prescribed because they are not included in our institutions enhanced recovery protocol.

As per the standardised enhanced recovery protocol clear liquids were allowed on the evening of surgery and on the first postoperative day patients were advanced from free fluids to soft diet when permitted. Mobilisation was encouraged the day of surgery and required the day after. Patients met the discharge criteria when they were comfortable on oral analgesia during full mobilisation, tolerated soft diet and had passed flatus or stool.

Study parameters

The primary endpoint was morphine consumption in the first 48 postoperative hours. Exact opioid consumption was recorded from the patient's drug chart and from PCA pump read-out.
Secondary outcome measures included visual analogue pain scores at rest and on activity (numerical rating scale from 0 (no pain) to 10 (most severe)), and postoperative nausea scores. Patient and nursing staff assessed pain scores separately at 6, 12, 24 and 48 hours after surgery.
Surgical outcome measures included: time to (out of room) mobilisation, time to pass first flatus and stool and length of hospital stay. Any complications were recorded.

Statistical analysis

Sample size calculation was based on a retrospective review of 44 patients undergoing laparoscopic bowel resection, which showed mean total morphine consumption in the first 48 postoperative hours of 67mg (44) (mean (SD)). Our hypothesis was that the TAP block would reduce the opioid use by 40 per cent [12]. Assuming a power of 80 per cent and a level of significance of 5 per cent, it was estimated that 33 patients would be required in each group. The sample size was derived from previously published tables, using the above values .[14] We decided to recruit 36 patients in each group to allow for conversion to laparotomy.

Statistical analysis was performed using Stata version 9.2. Distribution of continuous variables including the primary outcome, were assessed for approximation to the normal distribution (Shapiro-Wilk test) and for evidence of outliers. Normally distributed variables were summarised using the mean. Ordered categorical variables (visual analogue scores for pain (rest and movement) and nausea) and non-parametrically distributed metrics of recovery time (days to flatus, light diet, mobilisation and length of stay) were summarised using the median and inter-quartile range (IQR).

Patient characteristics, anaesthetic and surgical process indicators were compared between randomization groups, whilst comparison of primary and secondary outcomes excluded patients requiring conversion to laparotomy post-randomization (per protocol) and patients with incomplete measurement of outcomes.

Crude differences in PCA morphine use between anaesthetic procedures were estimated using the Student's t-test. Multivariable linear regression was used to estimate confounder adjusted differences in PCA morphine use, in the absence of model specification utilised forward selection (p <0.20). There was no evidence of heteroskedasticity or non-normality of residuals in null or fully specified models. Visual analogue scores and recovery time were analysed with the Mann-Whitney U-test, without adjustment. 95% confidence intervals and two-tailed p values were calculated.

RESULTS

Seventy-one patients were randomly assigned into the study. One randomization procedure was voided due to the absence of a randomization envelope. Fifteen patients initially randomized were subsequently excluded from analysis: eight cases required conversion to laparotomy, whilst seven cases had incomplete recording of outcomes measures: eight from the TAP block trial and seven from the LA group (Figure 1). Probability of exclusion due to open conversion **(P=0.629)** or missing outcome records **(P=0.781)** was not significantly different between randomization arms. In total, fifty-six patients both completed the study and had complete outcomes measures.

~~**Attempts were made to record the videos of the blocks. Due to problems with the technology we only collected 50% of the videos. The accuracy of the block placement were confirmed by an independent regional anaesthesia expert who reviewed the video, it was therefore unlikely that overall, block placement was deficient.**~~

Randomization groups were comparable in terms of age, sex, body mass index (BMI), ASA status and type of surgery (Table 1). Patient characteristics were also similar in analysed patients groups (Table 2). Postoperative complications in the analysed patient groups included one rectus sheath haematoma in the TAP-block group, one anastomotic leak in the LA-group, one anastomotic bleed in the LA-group and three prolonged ileus (one in TAP-block group and two in LA-group).

Time to mobilization, time to pass flatus or stool, time to start free fluids or light diet, and length of hospital stay did not show significant differences between the groups (Table 3). The visual analogue scores on pain at rest and activity were comparable between groups **(Table 4).** There was no significant difference in the VAS scores at activity and rest between the two groups over time. The total morphine requirements at 24 and 48 hours were similar in both groups **(P=0.750, Table 5). There was no difference in pain scores or morphine requirement between both groups in patients with prior minor abdominal surgery.** After adjusting for age, gender and type of operation

there was also no evidence for a difference in morphine requirements at 24 and 48 hours between randomization groups. There was statistical evidence that morphine requirements at 48 hours decreased with increasing age **(P<0.001).** Patients who had a postoperative complication appeared to have higher usage of morphine. However, neither altered the lack of association between TAP-block/local anaesthesia and PCA requirements at 48 hours.

DISCUSSION

This randomized controlled trial shows that in elective laparoscopic colectomies wound infiltration with LA has equal analgesic efficacy to TAP blocks **performed on induction**, **using Bupivacaine**, with regards to overall morphine consumption and pain scores in the first 48 hours postoperatively. Our finding, that the cumulative morphine use was positively correlated with postoperative complications and negatively correlated with increasing age, is consistent with the literature on this subject.[15]

Effective post-operative pain management is a prerequisite for any enhanced recovery program. Multimodal analgesic regimes are the gold standard and improve pain control by blocking differing pain pathways to reduce nociception and transmission.[1] Side effects related to toxicity of individual drugs are reduced because the amount of each agent required to achieve analgesia is less when it is used in combination with other agents.[16] Whilst the thoracic epidural traditionally had a key role in colorectal surgery, large randomized trials failed to show an absolute mortality benefit in major open abdominal surgery.[17,18] Their use is potentially limited by high failure rates, cardiovascular adverse effects, and rare but life changing procedure related complications.[19] Their role is being questioned in minimally invasive colorectal surgery with studies showing potential compromise of colonic mucosal and mesenteric arterial blood flow.[20] There is some evidence that epidurals may actually delay time to discharge in elective laparoscopic colorectal resections.[21] Opioids carry an increased risk of postoperative nausea and vomiting, ileus, urinary retention, sedation and respiratory depression and these side effects restrict their use within Enhanced Recovery Pathways.[1] The opioid sparing effects of Non-steroidal anti-inflammatory drugs have to be weighed against their theoretical effects on (anastomotic) healing and increased leakage rates.[22]

Peripheral nerve blocks may help reduce or avoid many of these side-effects and are a useful addition to the array of pain relief modalities**. Many different abdominal wall blocks can be utilised including rectus sheath blocks and catheters.[23] Intrathecal LA with opiate is also popular.[24]**

Ultrasound guided TAP blocks are simple to perform, provide abdominal wall analgesia and have a good safety profile and for this reason have been used for many years in our institution. The aim of all these blocks is to reduce postoperative opiate consumption, thereby reducing potential opiate side effects and enabling a better patient experience and an earlier discharge. There is little evidence to guide an anaesthetist in deciding which peripheral nerve block to use and so clinically a variety of abdominal wall blocks are used dependent on the anaesthetists preference and institutional protocol.

A few studies have demonstrated that TAP blocks are beneficial in reducing opioid consumption as well as pain scores when compared to inactive controls for laparoscopic colonic resections.[10,11,12,13] This is the first study to compare TAP blocks **using Bupivacaine** to the standard practice of LA wound infiltration in elective laparoscopic colorectal surgery. Studies comparing TAP blocks to wound infiltration in laparoscopic cholecystectomy[25] and hernia repair[26] also found no significant differences in pain scores, morphine use and recovery. On the other hand results in the gynaecological literature are mixed.[27]

Dose, volume and positioning of the LA are paramount in determining effectiveness. LA placed in the pre-peritoneal and sub-fascial spaces seems to have significantly better effects then subcutaneous/ superficial to the fascia .[28, 29] ~~**The relative success of wound infiltration in our study might be explained by the large volume (40ml, 0.25% Bupivacaine) of LA used.**~~ **The relative success of wound infiltration in our study might be explained by the fact that the TAP blocks are administered before the procedure and the local wound infiltration after, so the TAP group is put at a disadvantage.**

It's important to note that morphine consumption at 24 hours in the TAP group was similar to a previous study which demonstrated the benefit of TAP block when compared to inactive control for laparoscopic colonic resections and therefore TAP block was presumably effective as an analgesic modality in our study. [10] A second possibility could be that lateral TAP blocks as used in this study might be inferior to posterior TAP blocks. It has been suggested that posterior blocks via the triangle

of Petit may lead to a paravertebral spread of LA, [30] delivering a wider sensory block with longer lasting effects then the more anterior blocks.[31]

The effectiveness of any block is highly dependent on accurate delivery of the LA in the correct plane, in this case between the internal oblique and the transversus abdominis muscles.[5] Modification of the "blind'' landmark based technique to ultrasound guided approaches have led to higher accuracy and less complications.[32,33]

To ensure correct placement of the blocks in our study, all blocks were performed by one of three anaesthetists experienced in performing TAP blocks. All TAP blocks were performed under high resolution, real-time ultrasound and recorded for review and assessment. We chose not to perform abdominal wall sensitivity tests, as this would have interfered with patient blinding and may have influenced the overall results. Furthermore, the extent of sensory blockade may not necessarily reflect the analgesic effect of the TAP block.[31]

Equivalence between TAP block and LA infiltration might be explained by the relatively long interval of 48 hours for opioid consumption and pain levels that we studied. **Although the initial TAP studies demonstrated an analgesic effect for 24h,[9] prolonged analgesia up to 48 hours have been described for TAP blocks,[31] which is why we chose to study the first 48 hours postoperatively. As the TAP blocks were performed just before the start of the procedure and the wound infiltration at the end, this might have led to a decrease in effect of the TAP block, an important limitation in this study. However literature suggests that pre-incisional TAP blocks are more effective in (pre-emptive) pain control then post-incisional blocks.[34, 35]** A solution to this 'single-shot' problem might be continuous catheter infusion of LA in the TAP plane. First studies on this technique in abdominal surgery are very promising.[36, 37] However several trials also demonstrate excellent analgesic results after simple continuous wound infiltration following abdominal procedures. The benefits described include decreased opioid use, better pain control and shorter

hospital stay.[38, 39] The answer may be found in sustained release local anesthetics being developed that deliver up to 96 hours of analgesia and remove the need for an infusion device. [40]

In our study one patient in the TAP block group developed a rectus haematoma. ~~We were unable to determine whether this was a result of the TAP block or a surgical complication.~~ Ultrasound guided approaches have led to higher accuracy and less complications.[32,33] However, although rare, complications like internal organ damage and rectus sheath haematomas can occur.[41] Besides the intrinsic safety of wound infiltration, the simplicity and reliability of the technique are significant advantages. TAP blocks require a degree of expertise and skill and (costly) ultrasound equipment. Consequently it may be questioned whether a TAP block is justified in elective laparoscopic minimally invasive colonic resections.

One limitation of our study the small sample size. Although we powered the study appropriately based on initial observations of morphine use, the actual morphine use in the comparator (TAP block) group was much lower (this itself could have been a Hawthorne effect). Therefore, our expected reductions would have been much more modest, and required a higher sample size to detect any differences. Moreover, although we recruited the planned sample size, it was unfortunate that the losses to follow-up reduced the number reported. Nevertheless, the actual means of the two groups were so close in value that any detectable differences, even in a larger sample size, are likely to be very modest indeed. Ethics does not allow recruitment of more patients than planned, regardless of how many drop out. Nevertheless the data from the excluded patient might be included on an intention-to-treat analysis (as is regarded by some as conventional statistical handling for dropouts) but does not alter the results (because the means remain so close).

Another limitation is that the data sets are beyond the time in which Bupivacaine is indicated effective. Also, there may be other agents, such as liposomal Bupivacaine, that may or may not be effective that this paper does not prove or disprove.

In conclusion, in patients undergoing elective laparoscopic colonic resections, LA infiltration of port and extraction sites at the end of surgery is equivalent to bilateral ultrasound-guided TAP blocks performed on induction using the same concentration and volume of LA, in terms of total morphine consumption, pain control and recovery 6 hours after surgery.

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Figure 1 Flowchart of participants

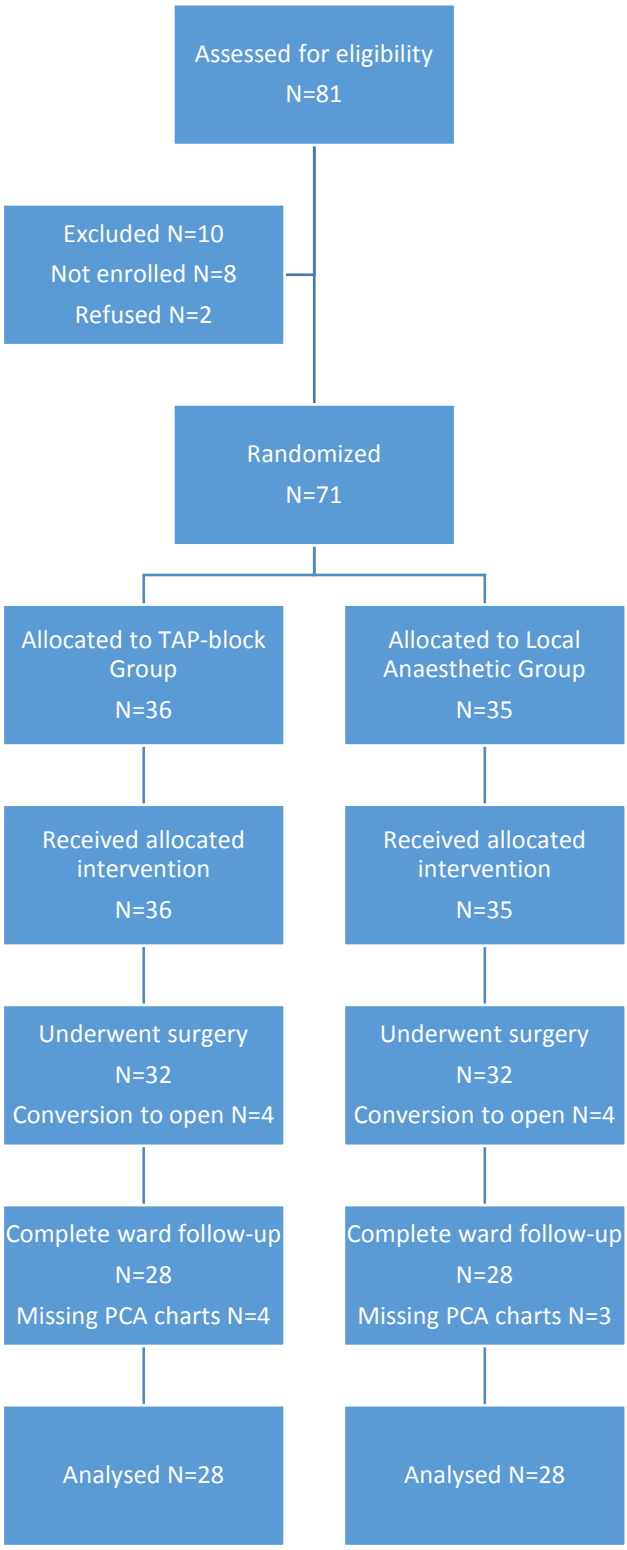

Table 1: Basic characteristics randomization groups

	TAP-block Group (N = 36)	**LA** Group (N = 35)	P- value
Age - yr. mean (CI)	68.7 (65.0 – 75.5)	67.8 (64.3 – 71.4)	P=0.718
Body Mass Index (BMI) kg m^{-2} mean (CI)	26.8 (22.9 – 27.2)	28.5 (24.6 – 29.1)	P=0.140
	number (percent)		
Gender Male Female	 20 (56) 16 (44)	 19 (54) 16 (46)	P=0.914
ASA classification I II III	 10 (28) 22 (61) 4 (11)	 5 (14) 28 (80) 2 (6)	P=0.219
Diagnosis of cancer	29 (81)	31 (89)	P=0.274
Previous Surgery	9 (25)	8 (23)	P=0.527
Surgical procedure Lap Right hemicolectomy Lap High anterior resection	 9 (25) 27 (75)	 11 (31) 24 (69)	P=0.638
Wound length: **cm** median(IQR)	6 (5-7)	5(4-6)	P=0.120
Conversion: **number** (percent)	4 (11)	4(12)	P=0.629
Duration operative procedure: **minutes** median (IQR)	180 (140 – 240)	200 (154 – 260)	P=0.425
Postoperative complications **number** (percent)	4 (11)	6 (17)	P=0.514

Table 2: Basic characteristics analysed groups

	TAP-block Group (N = 28)	**LA** Group (N = 28)	P- value
Age - yr. mean (CI)	67.6 (62.8 – 72.9)	68.0 (61.7 – 73.1)	P=0.885
Body Mass Index (BMI) kg m^{-2} mean (CI)	26.9 (22.4 – 27.3)	28.9 (24.4 – 29.3)	P=0.104
	number (percent)		
Gender Male Female	 16 (57) 12 (43)	 15 (54) 13 (46)	 P=0.788
ASA classification I II III	 8 (29) 18 (64) 2 (7)	 4 (14) 23 (82) 2 (1)	 P=0.280
Diagnosis of cancer	21 (75)	25 (89)	P=0.216
Previous Surgery	8 (29)	6 (22)	P=0.239
Surgical procedure Lap Right hemicolectomy Lap High anterior resection	 9 (32) 19 (68)	 5 (18) 23 (82)	 P=0.116
Wound length: **cm** median(IQR)	6 (5-7)	5(4-6)	P=0.188
Conversion: number (percent)	**3 (11)**	**5 (18)**	**P=0.226**
Duration operative procedure: minutes median (IQR)	**200 (150 – 230)**	**205 (160 – 240)**	**P=0.990**

Table 3 Time to event

	TAP-block Group (N = 28)	LA Group (N = 28)	P- value
Median time to get out of bed (95% CI) days	1 (0.5 -2.0)	1 (0.5-2.0)	P=0.966
Median time to pass flatus (95% CI) days	1 (0.5 -3)	1 (0.3 – 3)	P=0.118
Median time to pass stool (95% CI) days	2.5 (1-5)	3 (1-6)	P=0.402
Median time to start free fluids (95% CI) days	1.5 (0.5 – 3)	2 (0.5 – 4)	P=0.723
Median time to start light diet (95% CI) days	2 (1 – 5)	2.5 (1 – 6)	P=0.164
Median lenght of hospital stay (95% CI) days	4.5 (3 – 9)	4.5 (3 -8)	P=0.765

Table 4: Post-operative pain score, nausea score and mean PCA morphine consumption by randomization group. †Patient-reported, numerical rating scale from 0 (no pain) to 10 (most severe). CI, confidence interval; PCA, patient controlled analgesia.

	TAP-block Group		**LA** Group		P value
Mean cumulative PCA morphine					
	n	Mean (95% CI)	N	Mean (95% CI)	t test
<24 h (mg)	28	30.9 (24.0–37.8)	28	31.0 (24.1-37.9)	P=0.979
< 48 h (mg)	28	47.3 (36.2–58.5)	28	46.7 (36.2–57.3)	P=0.939
Pain and nausea scores†					
	n	Median (IQR)	N	Median (IQR)	Mann-Whitney U test : P-value
Pain score at 24 hours (rest)	25	2 (1 - 3)	25	2 (1 - 5)	0.672
Pain score at 24 hours (activity)	22	5 (2 - 7)	24	4 (2 - 7)	0.808
Nausea score at 24 hours	21	0 (0 – 0.5)	23	0 (0 – 0)	0.924
Pain score at 48 hours (rest)	21	1 (0.5 – 4.5)	23	2 (0 - 3)	0.820
Pain score at 48 hours (activity)	21	2 (1.5 – 5)	22	2 (1 - 5)	0.941
Nausea score at 48 hours	15	0 (0 - 0)	18	0 (0 – 0.25)	0.899
Time to recovery :days, median (IQR)					
Mobilization	26	1 (0.5 – 2)	28	1 (0.5 – 2)	0.908
Readiness for discharge	24	4.5 (3 – 9)	28	4.5 (3 – 8)	0.910

Table 5: Crude and adjusted morphine consumption by randomization group

	Difference in cumulative Morphine use at 48 hours (mg)					
	Crude			Adjusted		
	Difference (mg/48hr)	95% CI	p	Difference (mg/48hr)	95% CI	p
TAP vs. LA	+0.57	-14.4 to 15.55	0.939	+2.00	-10.52 to +14.51	0.750
Age (per year)	-1.21	-1.85 to -0.58	<0.001	-1.36	-1.97 to -0.76	<0.001
Post-operative complication (vs. none)	+20.77	0.13 to 41.4	0.049	+27.86	9.73 to 45.98	0.003

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