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Protocol Article

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# Optimal peripheral nerve block after minimally invasive colon surgery – a study protocol for a randomised trial

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## ABSTRACT

**INTRODUCTION** Transversus abdominis plane (TAP) blocks are used for post-operative pain management, but their efficacy remains unclear. We aim to investigate the effect of two TAP block methods in minimally invasive colon surgery.

**METHODS** This will be a double-blind, randomised and controlled multicentre trial including 360 adults who are planned for elective minimally invasive colon surgery with curative intent for colon neoplasia. The participants are randomised to one of three arms: active ultrasound-guided TAP (US-TAP) and placebo laparoscopic assisted TAP (L-TAP), placebo US-TAP and active L-TAP, or placebo US-TAP and placebo L-TAP. The primary outcome is morphine dose equivalents administered during the first 24 hours after surgery. Secondary outcomes are pain on the first post-operative day, length of stay, post-operative nausea and vomiting, and quality of recovery measured using the Quality of Recovery 15 questionnaire. Statistical analysis will determine any superiority of US-TAP and L-TAP versus placebo, and any non-inferiority of L-TAP compared with US-TAP. The latter will only be tested if superiority to placebo is shown. Primary and secondary outcomes will be analysed as intention-to-treat regarding superiority and as intention-to-treat and per protocol regarding non-inferiority.

**CONCLUSION** This will be the first ever blinded multicentre trial comparing L-TAP, US-TAP and placebo in daily clinical practice. The study has the potential to determine the role of the TAP in minimally invasive colon surgery.

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More than 2,500 Danish patients annually undergo elective colon surgery for malignant or benign diseases; and 80-90% of these procedures are performed as minimally invasive surgery (MIS). The implementation of MIS and enhanced recovery after surgery (ERAS) by an array of standardised protocols applied to all patients have improved post-operative outcomes including pain management, early mobilisation and bowel function, and have reduced length of stay (LOS) [1, 2].

Multimodal analgesic therapy is an important part of ERAS and may include regional or neuroaxial nerve blocks. As a part of the ERAS protocol, regional analgesia is associated with fewer post-operative opioid requirements and thus fewer and less intensive opioid-related adverse effects [3].

In some Danish centres, the transversus abdominis plane (TAP) block has been implemented as the primary analgesic modality in minimally invasive colorectal surgery [4-6]. Several techniques are currently used to apply TAP block, including blind injection using anatomical landmarks [7], ultrasound-guided (US-TAP) [8] and transcutaneous laparoscopic assisted TAP (L-TAP) blocks [5, 9, 10]. The L-TAP has several advantages, including ease of performance, less dependency on skills or equipment and avoidance of intraperitoneal injection [5, 9, 10].

A newly published meta-analysis comparing L-TAP with US-TAP, local infiltration analgesia (LIA) and placebo showed statistically significant but clinically negligible differences of 1-3 mg in the 24-hour morphine consumption between the groups [11]. Another meta-analysis investigating TAP block in laparoscopic colorectal surgery recorded similar results [12]. However, the studies included in the meta-analyses all had a population of fewer than 200 participants with an average of 93 and 69, respectively. The heterogeneity in populations, size and results questions the validity of the conclusions. The effect of TAP block is not convincing, though it is widely used, and larger multicentre randomised trials are warranted to confirm these findings and to determine whether TAP block is clinically relevant in minimally invasive colon surgery.

With this multicentre study, we aim to investigate 1) whether two different TAP techniques, i.e. US-TAP and L-TAP, are superior to placebo, and 2) whether L-TAP is at least as effective for pain management as US-TAP since L-TAP is easier, faster and more convenient to perform than US-TAP. The study population chosen consists of patients undergoing minimally invasive colon surgery. We hypothesise, firstly, that US-TAP and L-TAP are superior to placebo; secondly, that L-TAP is non-inferior to US-TAP. Both are determined by 24-hour morphine consumption after laparoscopic colon surgery using a pre-specified 10 mg margin.

## METHODS

### Design

The study is conducted as a multicentre prospective pragmatic trial in a daily clinical setting in five Danish colorectal centres with a three-arm (3:3:2), double-blind, randomised and placebo-controlled design.

### Eligibility criteria

The inclusion criteria are patients older than 18 years who are planned for elective MIS for colon cancer or adenoma with curative intent and without a planned ostomy. Rectal procedures are not included. The eligibility criteria are specified in **Table 1**.

**TABLE 1** Inclusion and exclusion criteria in the OPMICS trial.

| Criterion | Description |
|---|---|
| Inclusion | Patients planned to receive curative, elective, minimally invasive colon surgery for colon cancer or adenoma without a planned ostomy including the following procedures: laparoscopic ileocecal resection, laparoscopic right hemicolectomies, other type of laparoscopic resection of both small and large bowel, laparoscopic resection of transverse colon, laparoscopic left hemicolectomy, laparoscopic resection of sigmoid colon and other laparoscopic colon resections<br>≥ 18 yrs of age<br>Having given informed written consent |
| Exclusion | Known allergy to local anaesthetics<br>Known liver failure of Class C according to the Child-Pugh Score<br>Body weight < 40 kg<br>History of being a chronic pain patient: weekly intake WHO step II or step III or adjuvant step I analgesic [13]<br>Presence of concomitant painful conditions other than low back pain that may confound the subject's trial assessments or self-evaluation of the index pain, e.g., syndromes with widespread pain such as fibromyalgia<br>Predictably non-compliant due to language barrier or mental illness<br>Patients rescheduled for open surgery before the intervention has been administered<br>Patients where the indication for surgery changes before the intervention has been administered<br>Patients with known inflammatory bowel disease<br>Patients who have previously undergone open major abdominal surgery defined by prior intraabdominal surgery with a midline or upper abdominal incision of > 8 cm<br>Incisional hernia<br>Patients with a history of abdominal wall surgery including resection of the external oblique muscles, the internal oblique muscles, the transversus abdominis muscles, the rectus abdominis muscles or their fascial components<br>Pregnancy: patients are screened using u-hCG upon admission if female and not postmenopausal |

OPMICS = optimal peripheral nerve block after minimally invasive colon surgery; u-hCG = urine human chorionic gonadotropin.

### Randomisation and blinding

Patients are screened and enrolled preoperatively in the outpatient clinic by the surgeon responsible for the treatment. The investigator or a study staff member is responsible for obtaining informed consent and for participant inclusion. Randomisation and packaging of the trial medication into 15 blocks of 24 sealed opaque packages is done by the Pharmacy of the Capital Region of Denmark. Each block containing 24 sealed packages is allocated in a 3:3:2 ratio to one of the three following groups: 1) Active US-TAP, placebo L-TAP. 2) Placebo US-TAP, active L-TAP. 3) Placebo US-TAP, placebo L-TAP.

Randomisation of participants occurs upon collection of the packed medicine prior to surgery. Participants are allotted a randomisation number according to the sealed package. Physicians, nurses, caretakers, participants and study personal are all blinded to the intervention given.

### Interventions

Active medication consists of 2 × 20 ml ropivacaine 2 mg/ml corresponding to 80 mg of ropivacaine. Placebo

consists of 2 × 20 ml sodium chloride 9 mg/ml solution. The ampules containing ropivacaine and placebo are similar in packaging, colour and consistency. Besides the randomised medication, each package contains two 20 ml ampules, one with ropivacaine 2 mg/ml and one with sodium chloride 9 mg/ml solution to increase volume if needed, for LIA around the bowel extraction site. The ampules are marked with US-TAP, L-TAP or wound infiltration.

Each patient receives a maximum 120 mg dose of ropivacaine corresponding to the maximum dosage for a person weighing 40 kg. Besides the given intervention, all patients will receive the standard pre- and post-operative care within the local ERAS regimens including post-operative pain treatment with standard paracetamol 1 g four times daily supplemented by opioids as needed. Before surgery, participants are required to answer three surveys (the Hospital Anxiety and Depression Scale [14], the Pain Catastrophizing Scale [15] and the Quality of Recovery 15 (QoR-15) [16]). On the first post-operative day, the patients are asked to answer questions according to study outcomes, including the QoR-15 survey. Patients who refuse to participate in the trial or who are excluded in accordance with the exclusion criteria will receive the standard treatment.

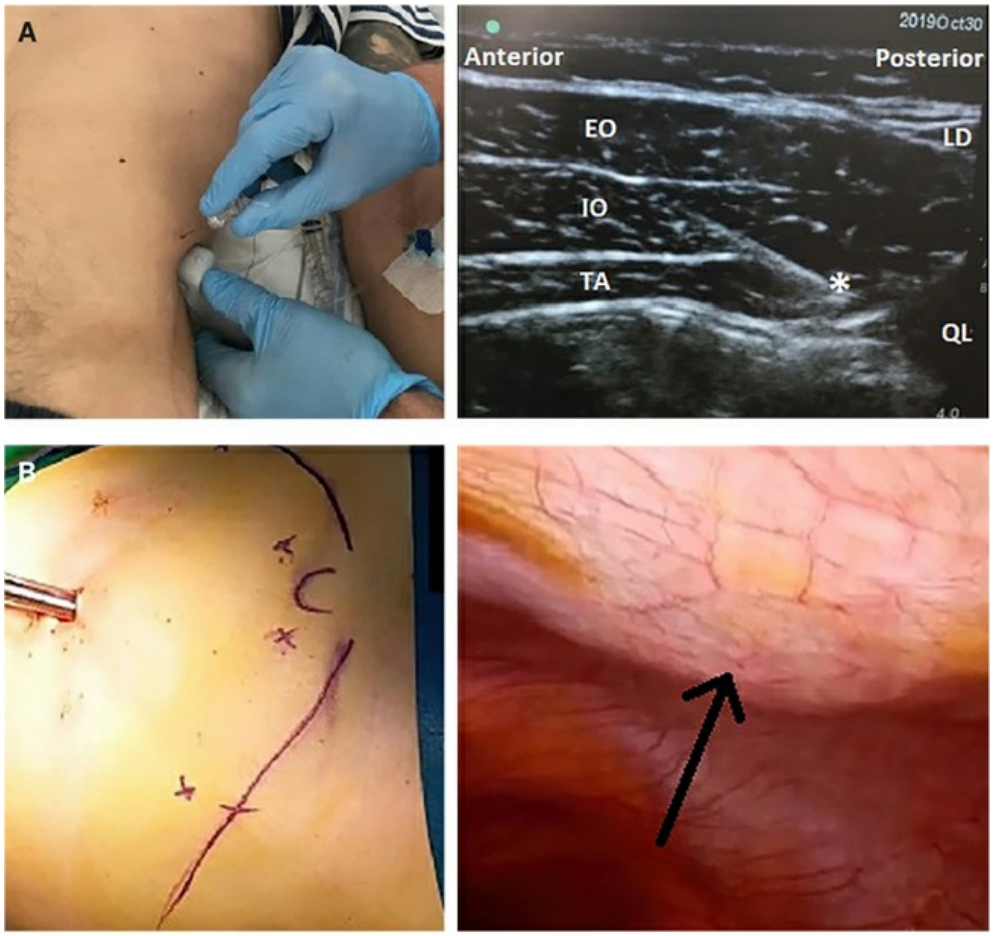
A 30-day follow-up based on review of the electronic medical record will be performed to determine LOS and any complications or side effects that the patient may have experienced.

**Ultrasound-guided posterior transversus abdominis plane block**

US-TAP is applied before surgery to achieve the shortest possible time difference between application of US-TAP and L-TAP. After intubation and just prior to sterile draping, an anaesthesiologist trained in the procedure applies the US-TAP corresponding to the posterior TAP method described below.

With the patient in supine position, the three layers of the abdominal wall musculature are identified using a linear high-frequency transducer placed perpendicularly to the body's longitudinal axis in the flank approx. 2.5 cm cranially to the anterior superior iliac spine. The neurovascular plane is located between the internal oblique and transverse abdominal muscles. A 90-120 mm 21-gauge needle is used, and the correct position of the needle tip is 1 cm anteriorly to the tapering of the fascia layers into the thoracolumbar fascia. A small amount of study medication is injected to visualise the spread of the fluid in the correct plane. Injection is administered bilaterally (**Figure 1**).

**FIGURE 1** Techniques used to apply the posterior ultrasound-guided transverse abdominis plane block and the anterior laparoscopic-assisted transverse abdominis plane block. **A**. Ultrasound probe position, needle puncture site and sonographic image of the posterior transversus abdominis plane block. **B**. Puncture sites and laparoscopic visualisation of a bulge (arrow) during application of laparoscopic-assisted transverse abdominis plane.




EO = external oblique muscle; IO = internal oblique muscle; LD = latissimus dorsi; TA = transversus abdominis; QL = quadratus lumborum.

**Laparoscopically assisted anterior double transversus abdominis plane block**

Once the application of the US-TAP is concluded, sterile draping is applied and the surgeon proceeds with intraperitoneal laparoscopic access. The placement of the first laparoscopic port is immediately followed by the application of the L-TAP (sub-costal/anterior dual TAP block). A total of four injections are given, each with 10 ml of study medication: bilateral subcostal injections between the mid-clavicular and the midline and bilateral subcostal injections between the mid-clavicular and anterior axillary lines (Figure 1).

The needle tip is visualised laparoscopically passing into the preperitoneal fat without perforating the parietal peritoneum. The needle is then withdrawn a few millimetres, so that the tip is located just superficially to the

posterior rectus sheath/the transverse abdominis fascia and the injection is administered. Confirmation of the correct plane can be visualised by the formation of a bulge covered by the transverse abdominal muscle fascia (Figure 1).

**Outcomes**

The primary outcome is total morphine dose in intravenous mg equivalents administered within the first 24 hours after arrival to the post-anaesthesia care unit. Morphine dose equivalent conversion is done using the rates provided in **Table 2** [17]. Secondary outcomes are specified in **Table 3**.

**TABLE 2** Morphine dose equivalents for different opioids used in the OPMICS trial. The values are mg.

| | Route of administration | | |
|---|---|---|---|
| Opioid | intravenous or other parenteral | oral | rectal |
| Morphine | 10.0 | 30.0 | 30.0 |
| Alfentanil | 1.0 | - | - |
| Fentanyl | 0.1 | - | - |
| Ketobemidone | - | 15.0 | - |
| Oxycodone | 7.5 | 20.0 | - |
| Tramadol | - | 150.0 | - |

OPMICS = optimal peripheral nerve block after minimally invasive colon surgery.

**TABLE 3** Study outcome measures in the OPMICS trial.

| Type | Outcome |
|---|---|
| Primary outcome | Total morphine dose in IV equivalents in mg administered in the first 24 h from the end of anaesthesia |
| Secondary outcomes | Total morphine dose in IV equivalents administered in the operating theatre at the end of surgery not including remifentanil<br>Total morphine dose in IV equivalents administered in the PACU<br>Post-operative pain at rest: 08:00-10:00 a.m. POD 1<br>Post-operative pain when coughing: POD 1<br>Post-operative length of stay measured from the end of anaesthesia<br>Incidence of post-operative nausea and vomiting: POD 1<br>Total dose of antiemetic medication administered in the first 24 h from the end of anaesthesia<br>Total dose of antiemetic medication administered in the operating theatre<br>Time spent in the PACU<br>Post-operative mobilisation: POD 1<br>Quality of recovery-15 POD 1 – Danish version [16]<br>Post-operative complications during the first 30 PODs according to the Clavien-Dindo classification of surgical complications [18]<br>Need for rescue transversus abdominis plane block or epidural analgesia |

IV = intravenous; OPMICS = optimal peripheral nerve block after minimally invasive colon surgery; PACU = post-anaesthesia care unit; POD = post-operative day.

### Statistics

*Sample size calculation*

To estimate the number of participants needed to determine whether US-TAP and L-TAP are superior to placebo, we chose the following parameters: a two-sided statistical significance level of 0.05/2 = 0.025, a power of 0.80 and a difference in 24-hour post-operative morphine consumption of 10 mg between intervention and placebo with a standard deviation (SD) of ± 20 mg. With these assumptions, 77 participants eligible for analyses are needed in each group [19, 20].

Based on our hierarchical design, non-inferiority analysis will be conducted only if the superiority of both TAP blocks against placebo is confirmed. To establish non-inferiority of L-TAP versus US-TAP, we chose a non-inferiority margin of 10 mg (SD: ± 20) 24-hour post-operative morphine consumption. This margin was based on clinical relevance. Furthermore, we chose a two-sided statistical significance level of 0.05/4 = 0.0125 (because it is the third analysis). A power of 0.90 was chosen because of the non-inferiority design. With these assumptions, 105 patients eligible for analyses must be included in both TAP groups. An estimated 10-20% of patients will be converted to open surgery or stoma creation. To compensate for this and allow for loss to follow-up, dropouts and the requirements of both intention-to-treat and per protocol analyses, we plan to include 90 patients in the placebo group and 135 patients in the US-TAP and in the L-TAP groups.

*Statistical analyses*

Data suited for statistical analyses will be analysed using R version 3.6.1 or later. A p-value of less than 0.05 is considered statistically significant; however, because of the hierarchical design of the study, Bonferroni correction has been applied for the primary outcome with statistical significance levels as stated previously. Continuous outcomes will be analysed by general linear models (logarithmic transformation of outcomes may be

used in order to comply with the model assumptions of parametric models). Binary outcomes will be analysed by logistic regression. Statistical model assumptions will be checked by residual diagnostics. In case of violation of model assumptions, non-parametric models will be used. Primary and secondary outcomes will be analysed as intention-to-treat regarding superiority and as both intention-to-treat and per-protocol regarding non-inferiority.

**Inclusion, centres and timeline**

Participants will be included in five Danish colorectal centres (Copenhagen University Hospital - North Zealand Hospital, Regional Hospital West Jutland, Regional Hospital Central, Hospital South West Jutland and Copenhagen University Hospital – Amager and Hvidovre Hospital). Each hospital is expected to include two patients weekly corresponding to an estimated total number of 360 participants. Participant inclusion began in January 2021 and follow-up is expected to conclude in March 2022.

**Data-sharing statement**

After de-identification, individual participant data will be made available to investigators who provide a methodologically sound proposal for meta-analyses.

**Ethics and data management**

The trial has been approved by the Ethics Committee of the Capital Region of Denmark (registration number: H-20026773), the Danish Medicines Agency and registered with the European Union Drug Regulating Authorities Clinical Trials Database (registration number: 2020-001054-22). Data management is approved by the Data Protection Agency of the Capital Region (registration number: P-2020-947). The study is conducted in accordance with Danish legislation and international good clinical practice guidelines for clinical trials on pharmaceutical products; and is monitored by the local regional GCP-units.

*Trial registration:* ClinicalTrials.gov: NCT04311099.

## DISCUSSION

Implementation of laparoscopic surgery and standardised ERAS protocols has significantly improved patient outcomes. Focus on multimodal pain management may potentially further improve these outcomes. Since the introduction of US-TAP, many reports have been published but no consensus has been reached regarding the optimal technique, where to and when to apply the block or which drug to use. By optimising post-operative pain management with peripheral nerve blocks, we may potentially improve important clinical outcomes, e.g. post-operative opioid consumption and pain. Metanalyses have shown statistically significant reductions in opioid consumption when TAP is compared with wound infiltration or placebo [11, 12], but the reported reductions of 1-3 mg in opioid consumptions have no clinical relevance. To ensure generalisability, we have designed a pragmatic multicentre trial to determine the clinical efficacy of TAP in minimally invasive colon surgery.

Our study design has several limitations including the (limited) time interval separating US-TAP and L-TAP application and that both are applied at the beginning of surgery. This might reduce the post-operative effect in case of a long surgery duration. However, no evidence exists that timing of application affects outcomes [11]. Another limitation is dosage. We have designed the study with a set dose that matches the maximum dosage for a person weighing 40 kg. This may potentially lessen the effect in obese patients. However, there is no evidence in the existing literature of optimal dosage [12]. The set dose will also provide us with data for post-hoc analyses of a potential dose-effect relationship.

This study will be the first blinded multicentre trial comparing L-TAP, US-TAP and placebo in daily clinical practice. Potentially, our results may bring evidence closer to a definitive conclusion as to the role of the TAP in

minimally invasive colon surgery.

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