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A prospective study evaluating the new local infiltration analgesia protocol for fast-track primary total knee arthroplasty at UNN Tromsø

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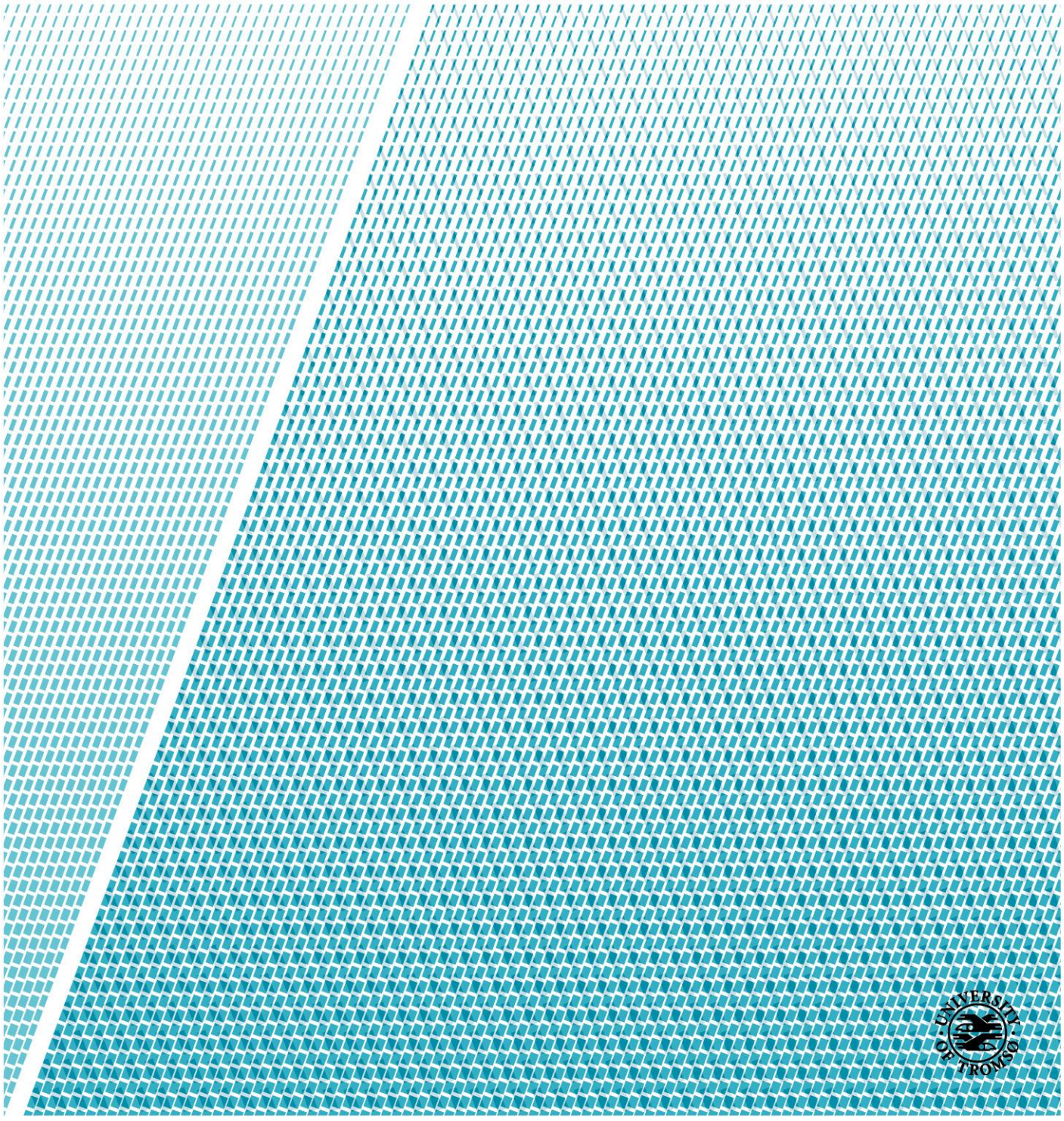

Preface

All health care professionals are responsible to ensure that all patients in their field receive care according to the highest standards. As a health care professional, it is not sufficient to ask, “what is the right thing to do?” We must also ask, “are we doing the right thing in the right way?” To ensure that all patients receive the highest quality of care, patient treatment needs to be continuously reviewed and improved.

This master thesis was written as part of the subject MED-3950 at the University of Tromsø The Arctic University of Norway and is my contribution to improving the quality of care for patients receiving fast-track primary total knee arthroplasty at UNN Tromsø.

The results from this master thesis were presented at the annual meeting of the Norwegian Society of Anaesthesiology in October 2017. The travel- and hotel costs related to this meeting were covered by The Surgical- and Critical Care Clinic at UNN Tromsø. The master thesis received no additional financial funding.

I would like to thank my supervisor professor Lars Marius Ytrebø for inspiring me to this project and for guidance and support throughout the entire process. I would also like to thank the nurses at the Post-anaesthesia care unit and Orthopaedic ward at UNN Tromsø that contributed to the prospective study performed in this master thesis.

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Contents

Abstract

Introduction: A new local infiltration analgesia (LIA) protocol was implemented for fast-track primary total knee arthroplasty (TKA) at UNN Tromsø in January 2017. The objective of this master thesis was to evaluate the new protocol, as well as postoperative pain, postoperative nausea and vomiting (PONV) and patient satisfaction following fast-track primary TKA at UNN Tromsø.

Materials and methods: A prospective study was performed at UNN Tromsø running from 12 January 2017 until 20 June 2017. All patients who received fast-track primary TKA at UNN Tromsø during the study period were included. Data concerning adherence to the new protocol was collected from the electronical health record. Postoperative pain, PONV and patient satisfaction were assessed at seven points during the first 24 hours postoperative using a specific pain- and satisfaction form.

Results: 28 patients were recruited to the study and included for analysis. Only three patients received premedication according to the new protocol and only nine patients received postoperative medication according to the new protocol. Most patients received too low dose of LIA according to the new protocol and timing of antibiotic prophylaxis was wrong in many of the patients. Median postoperative resting pain level (NRS) ranged 0-4 during the first 24 hours postoperative. A total of seven patients reported severe pain (NRS ≥ 7) at one or more of the assessments. The highest incidence of PONV was recorded in six patients at two separate assessments. Patient satisfaction was generally high, but four patients were unsatisfied with their patient journey.

Conclusion: Adherence to the new LIA protocol for fast-track primary TKA at UNN Tromsø was low. Despite low adherence to the new protocol patient satisfaction following fast-track primary TKA at UNN Tromsø was high. Postoperative pain scores and PONV following fast-track primary TKA at UNN Tromsø were acceptable but may be improved with increased adherence to the new protocol.

Glossary and abbreviations

ASA-classification	American Society of Anesthesiologists Classification.
Bds	Bis die sumendum, “two times a day”.
BMI	Body mass index (kg/m^2).
EHR	Electronical health record.
Fast-track surgery	A multimodal approach to patient care using evidence-based perioperative interventions aiming to enhance postoperative recovery, decrease morbidity and convalescence as well as reduce length of hospital stay.
FNB	Femoral nerve block.
Intraoperative	Relating to the time during a surgical procedure.
LIA	Local infiltration analgesia. Pain management technique involving intraoperative administration of a local anaesthetic in various combinations with epinephrine, nonsteroidal anti-inflammatory drugs, opioids and steroids to the surgical wound.
NPR-number(s).	Norwegian patient registry number(s).
NRS	Numeric rating scale. Used to measure pain and ranges from “0” (no pain) to “10” (worst pain imaginable).
NSAIDS	Nonsteroidal anti-inflammatory drugs.
Opioid naive	Patient not using any opioids upon hospitalization.
PACU	Post-Anaesthesia Care Unit.
Perioperative	Relating to the time before, during, and after a surgical procedure.
PJI	Prosthetic joint infection.
PONV	Postoperative nausea and vomiting.
Postoperative	Relating to the time after a surgical procedure.
Preoperative	Relating to the time before a surgical procedure.

Primary TKA	Primary total knee arthroplasty. The first total knee arthroplasty performed on a specific knee joint.
Prn	Pro re nata, “as needed”.
PROSPECT working group	Procedure specific postoperative pain management working group.
Revision TKA	Revision total knee arthroplasty. An additional total knee arthroplasty performed on a specific knee joint after a primer total knee arthroplasty have been performed.
TKA	Total knee arthroplasty.
Qds	Quater die sumendum, “four times a day”.

1 Introduction

1.1 Total knee arthroplasty

The normal knee joint functions as a complex hinge, primarily allowing flexion and extension but also some rotation and gliding. The knee joint consists of three compartments: medial, lateral and patellofemoral. The articular surfaces of each compartment are covered with cartilage that provides a smooth, lubricated surface for articulation and facilitates transmission of loads to the underlying subchondral bone. However, osteoarthritis, inflammatory arthritis, avascular necrosis, tumours, or congenital deformities may cause damage to the cartilage and a subsequent deterioration of its function (1). This may lead to one or more of the compartments needing replacement. Replacing one or more of the compartments can be performed with an orthopaedic procedure called knee arthroplasty. Knee arthroplasties can be either partial (unicompartmental) or total (bi- or tricompartmental).

Total knee arthroplasty (TKA) is a major orthopaedic procedure that involves a resection of the diseased cartilage and articular surfaces of the medial- and lateral compartment followed by a resurfacing with fitted metal- or polyethylene prosthetic components. In addition, a resection and resurfacing of the patellofemoral compartment may also be performed. The first TKA performed on a specific knee joint is called primary TKA. Additional TKAs performed on the same knee joint are called revision TKAs. If successful, primary TKA can lead to pain relief, to restoration of mobility and to improved quality of life (2).

The incidence of primary TKA in Norway has increased progressively over the last few years (3). In 2016 about 5500 primary TKAs were performed in Norway, making it a common orthopaedic procedure (3). The main reason for performing primary TKA is idiopathic osteoarthritis. In 2016 more than 90% of the primary TKAs performed in Norway reported idiopathic osteoarthritis as underlying cause for the procedure (3). Primary TKA is most often received by elderly patients. In 2016 more than 80% of patients who received primary TKA in Norway were above 60 years old (3).

1.2 Anaesthesia and analgesia for primary TKA

Despite the beneficial long-term effects of primary TKA (2), the procedure is associated with severe early postoperative pain and effective analgesia is therefore paramount (4). However, most patients who receive primary TKA are elderly. As a result, many of the patients receiving primary TKA will also have comorbid diseases. Thus, providing adequate anaesthesia and analgesia while keeping side effects to a minimum is challenging. Optimal perioperative analgesia will enhance functional recovery, including timely recovery of knee mobility, and reduce postoperative morbidity (4, 5).

In 2008 the Procedure Specific Postoperative Pain Management (PROSPECT) working group published evidence-based consensus recommendations for effective management of postoperative pain following primary TKA (4). General anaesthesia or spinal anaesthesia with local anaesthetic combined with femoral nerve block (FNB) was recommended as primary technique for surgery and postoperative pain. Paracetamol and conventional non-steroidal anti-inflammatory drugs (NSAIDS) or COX-2-selective inhibitors, plus intravenous (iv) strong opioids (high-intensity pain) or weak opioids (moderate- to low-intensity pain), together with cooling and compression techniques, were recommended as supplement to general- or spinal anaesthesia in combination with FNB.

Since 2008 research on postoperative pain management following primary TKA has progressed. Over the last few years local infiltration analgesia (LIA) has been increasingly used. LIA is a simple surgeon-administered technique that involves intraoperative administration of a local anaesthetic in various combinations with epinephrine, NSAIDS, opioids and steroids to the surgical wound. LIA is effective for managing acute postoperative pain following primary TKA (6, 7), and provides similar analgesia compered to FNB (8). However, LIA might be preferable over FNB following primary TKA due to the simple administration technique and the increased risk of falling associated with FNB (9). In addition to LIA, recent research has shown that administration of intraoperative high-dose iv corticosteroids reduces postoperative pain and postoperative nausea and vomiting (PONV) following primary TKA (10).

1.3 New LIA protocol for fast-track primary TKA at UNN Tromsø

A new anaesthesia protocol containing LIA (hereinafter referred to as "new protocol") for fast-track primary TKA was implemented at UNN Tromsø 31 January 2017 (appendix A). Fast-track surgery uses a multimodal approach to patient care using evidence-based perioperative interventions aiming to enhance postoperative recovery, decrease morbidity and convalescence as well as reduce length of hospital stay. This multimodal concept of fast-track surgery has shown substantial success for primary TKA and lead to reduced morbidity and length of hospital stay (11).

The new protocol included spinal anaesthesia with local anaesthetic as primary technique to provide adequate anaesthesia. To provide adequate analgesia the new protocol included multimodal pain management with paracetamol, NSAIDs and opioids given both preoperative and postoperative, as well as LIA and high-dose iv corticosteroids intraoperatively. Additionally, the new protocol also included several measures not aimed at analgesia and anaesthesia e.g. thromboembolic prophylaxis, antibiotic prophylaxis, bleeding prophylaxis, choice of equipment, patient monitoring etc.

Nurses and physicians at the Anaesthesia Department, Postoperative Care Unit (PACU) and Orthopaedic ward were responsible for ensuring that patient treatment was given according to the new protocol.

1.4 Objective of the master thesis

The objective of this master thesis was to evaluate the new protocol for fast-track primary TKA at UNN Tromsø. The following research questions were defined:

- Assess adherence to the new protocol for fast-track primary TKA at UNN Tromsø.
- Assess postoperative pain, PONV and patient satisfaction following fast-track primary TKA at UNN Tromsø.

2 Materials and methods

2.1 Study design

A prospective study was performed at UNN Tromsø running from 12 January 2017 until 20 June 2017. The study was commenced 19 days before the new protocol was officially implemented. However, clinical practise for fast-track primary TKA at UNN Tromsø was already adapted to the new protocol by study start. Thus, all patients who received fast-track primary TKA at UNN Tromsø during the study period were treated in accordance to the new protocol.

2.2 Study population

All patients who received fast-track primary TKA at UNN Tromsø during the study period were included in the study and analysis.

2.3 Data collection

2.3.1 Paint- and satisfactory form

A specific pain- and satisfaction form (hereinafter referred to as "form") was made for data collection (appendix B). Data from all patients included in the study were collected using this form. Assessments were performed seven times during the first 24 hours postoperative by nurses at the PACU and Orthopaedic ward or by author Arnstein Berg at the following time points:

1. Arrival PACU (0 hours postoperative)
2. 1 hour postoperative
3. 2 hours postoperative
4. Discharge PACU
5. Arrival Orthopaedic Ward
6. Evening operation day (8 hours postoperative)
7. Postoperative day 1 (24 hours postoperative)

The form consisted of five questions concerning postoperative pain, two questions concerning PONV and one question concerning patient satisfaction. To measure pain a

numeric rating scale (NRS) ranging from “0” (no pain) to “10” (worst pain imaginable) was used. The questions on the form are shown below (please note that the questions have been translated from Norwegian to English):

Postoperative pain

- Pain at rest (NRS 0-10)?
- If current resting pain, where is the worst pain focus located (anteriorly, medially, laterally, posteriorly or globally)?
- Maximal resting pain since last assessment (NRS 0-10)?
- Minimal resting pain since last assessment (NRS 0-10)?
- Average resting pain since last assessment (NRS 0-10)?

PONV

- Nausea now or since last assessment (yes/no)?
- Vomiting now or since last assessment (yes/no)?

Patient satisfaction

- Current satisfaction (Very unsatisfied, unsatisfied, satisfied, more than satisfied, very satisfied)?

Early in the study period the three questions concerning maximal-, minimal- and average resting pain since last assessment were removed from further data collection and excluded from analysis. This was done because the patients included in the study could not accurately recall the level of pain experienced in the periods between each assessment.

When assessed for postoperative pain, some patients were assigned NRS scores with decimal numbers e.g. NRS 4,5. Some patients were also assigned NRS scores using two numbers e.g. 4-5 or 4/5. In the analysis, all NRS scores with decimal numbers or two numbers were rounded up to the nearest whole number.

Some of the patients included in the study who were asked to locate the worst pain focus could not limit their answer to only one of the anatomical categories. For example, some

patients described the worst pain focus to be located anteromedially instead of anteriorly or medially. Therefore, new anatomical categories were constructed during analysis based on clinical relevance. Patients who located the worst pain focus anteriorly, medially or anteromedially were categorised having an “anteromedial worst pain focus”. Patients who located the worst pain focus posteriorly were categorised having a “posterior worst pain focus”. Patients who did not locate the worst pain focus anteriorly, medially, anteromedially or posteriorly were categorised having “other worst pain focuses”.

When assessed for current satisfaction, most patients had difficulty distinguishing between the categories indicating various levels of satisfaction and unsatisfaction. This created uncertainty regarding the difference between the categories used to measure patient satisfaction. Because of this uncertainty the various levels of satisfaction were combined into one category called “satisfied” and the two categories indicating various levels of unsatisfaction were combined into one category called “unsatisfied”.

The two questions concerning PONV on the form were combined during analysis to “Nausea/vomiting now or since last assessment”. This was done because there were few incidents of vomiting during the study period. The combined PONV question used in analysis was answered with “yes” if one or both of the original PONV questions on the form were answered with “yes”.

2.3.2 Electronic health record

Demographics and data concerning adherence to the new protocol were collected from the electronical health record (EHR) DIPS Arena. The EHR-data was collected by the author Arnstein Berg with the help from mentor Lars Marius Ytrebø. Adherence to the new protocol was scrutinized and discussed with professor Ytrebø. However, the final decision regarding protocol adherence was made by professor Ytrebø.

<u>Demographics collected from the EHR:</u>

- Sex
- Age

- Body mass index (BMI)
- Classification according to the American Society of Anesthesiologists (ASA-classification)
- Preoperative opioid use (opioid-naive defined as not using any opioids upon hospitalization)
- Knee (left/right)

Preoperative measures according to the new protocol assessed for adherence:

- Thromboembolic prophylaxis with dalteparin
- Premedication:
  - Oral Paracetamol 1000 mg for patients <70 kg or 2000 mg for patients >70 kg
  - Oral sustained-release naproksen 500 mg/ esomeprazol 20 mg
  - Oral sustained-release tapentadol 50 mg. Alternatively for patients >70 years oral sustained-release oksykodonhydroklorid 10 mg
  - No preoperative benzodiazepines
- Preoperative bladder emptying controlled and documented in the anaesthesia record by Orthopaedic ward nurse

Intraoperative measures according to the new protocol assessed for adherence:

- Spinal anaesthesia with bupivacaine 0,5% plain.
- Antibiotic prophylaxis with cefalotin 2 g iv qds according to national guidelines (12). First dose 30-60 minutes before the procedure, second dose 90 minutes after the first dose, then 2 g every 90 minutes up to four doses in total.
- Tranexamic acid 10 mg/kg intravenously if no contraindications. First dose 15 minutes before tourniquet is released. Second dose 3 hours after first dose.
- Dexametasone 16 mg iv.
- LIA with ropivacaine 2 mg/ml with adrenalin 5 µg/ml (total volume 120-150 ml).

Postoperative measures according to the new protocol assessed for adherence:

- Postoperative medication:

- Oral Paracetamol 1000 mg qds or 1500 mg qds.
- Oral sustained-release naproksen 500 mg/ esomeprazol 20 mg bds.
- Oral sustained-release tapentadol 50 mg bds.
- Iv Morphine or oral oksykodonhydroklorid 5 mg prn.

2.5 Data management and statistic

Data collected from the EHR was stored using Norwegian Patient Registry numbers (NPR-numbers). All non-electronical data, including the forms, were securely kept in a locked office at UNN Tromsø.

IBM SPSS Statistics 24 was used to produce descriptive statistics of the data collected. Missing patient data were excluded pairwise during analysis.

2.6 Ethics

Necessary approval from the data protection officer at UNN Tromsø was secured in advance of the study (appendix C). The study qualified as an internal quality assurance study. Thus, no additional approval from the regional committee for medical and health research ethics was required.

3 Results

28 patients were recruited to the study and all patients were included in the analyses. Demographic data are shown in Table 1.

3.1 Adherence to the new protocol

Data on adherence to preoperative measures are presented in Table 2. Premedication was received by three patients according to the new protocol. Most patients received too low dose of preoperative paracetamol and half of the patients did not receive preoperative naproksen/ esomeprazol. Preoperative tapentadol or oksykodonhydroklorid was received by most patients. Preoperative bladder emptying was usually controlled, but often not documented correctly. All patients received thromboembolic prophylaxis according to the new protocol.

Data on adherence to intraoperative measures are presented in Table 3. Spinal anaesthesia was received by 26 patients. The remaining two patients received general anaesthesia. LIA was received by 26 patients, but most patients received a lower dose than stated by the new protocol. Half of the patients did not receive dexametasone according to the new protocol. All patients received tranexamic acid, but two patients received the second dose at the wrong time.

Data on adherence to antibiotic prophylaxis are presented in Table 4. All patients received the first and second dose of prophylactic antibiotics and nearly all patients received the third and fourth dose with prophylactic antibiotics. However, most patients received the doses of prophylactic antibiotics at the wrong time according to national guidelines.

Data on adherence to postoperative measures are presented seen in Table 5. Only nine patients received correct postoperative medication. Nearly all patients received postoperative paracetamol, but half of the patients did not receive postoperative Naproksen/ Esomeprazol. 18 patients received postoperative Tapentadol.

3.2 Postoperative pain, PONV and patient satisfaction

Figure 1 shows a box-plot displaying the postoperative pain scores. Median resting pain level (NRS) at arrival in the PACU, 1 hour postoperative and 2 hours postoperative was 0. Median resting pain level at discharge from the PACU and arrival at the Orthopaedic ward was 2. Median resting pain level at evening operation day and postoperative day 1 was 4. A total of seven patients reported severe pain (NRS ≥ 7) at one or more assessments.

The locations of the worst pain focus are presented in Table 6. Maximum pain was usually located anteromedially. Few patients reported severe pain at the back of the knee joint.

Few patients reported PONV (Table 7). The highest incidence of PONV was reported by six patients at the evening operation day and postoperative day 1.

Satisfaction score is presented in Table 8. Patient satisfaction was in general high. However, four patients were unsatisfied with their patient journey.

4 Discussion

The results from this study showed that adherence to the new protocol for fast-track primary TKA at UNN Tromsø was disappointingly low. However, patient satisfaction was high. The incidence of postoperative pain and PONV following fast-track primary TKA at UNN Tromsø were relatively low, yet there are still room for significant improvements.

4.1 Adherence to the new protocol

Only three patients received premedication according to the new protocol. This was mainly due to patients receiving too low dose of preoperative paracetamol and not receiving preoperative naproksen/ esomeprazol. The new protocol stated that patients < 70 kg should receive 1000 mg oral paracetamol preoperatively and that patients > 70 kg should receive 2000 mg oral paracetamol preoperatively. No documentation was found as to why most patients received too low dose of preoperative paracetamol. One possible explanation might be that the physicians prescribing premedication were unaware that patients > 70 kg should receive 2000 mg oral paracetamol preoperatively instead of the standard dose of 1000 mg. This may have led to most patients receiving the standard dose of 1000 mg paracetamol regardless of weight. An initial dose of 2000 mg oral paracetamol is likely to achieve earlier meaningful plasma concentrations than 1000 mg, is considered safe and may lead to improved postoperative pain (13, 14). Thus, the fact that most patients in this study received too low dose of preoperative paracetamol may have led to increased postoperative pain.

In addition to most patients receiving to low dose of preoperative paracetamol, half of the patients did not receive preoperative naproksen/ esomeprazol. One patient did not receive preoperative naproksen/ esomeprazol due to allergy. However, no documentation was found as to why the remaining 12 patients did not receive preoperative naproksen/ esomeprazol. This may have been due to contraindications such as allergy or severe liver-, heart- or kidney impairment. However, it may also have been due to unawareness of the new protocol. The fact that half of the patients did not receive preoperative naproksen/ esomeprazol may have led to increased postoperative pain.

In contrary to preoperative paracetamol and naproksen/ esomeprazol, most patients received preoperative tapentadol or oksykodonhydroklorid. However, six patients did not receive preoperative tapentadol or oksykodonhydroklorid. As with preoperative paracetamol and naproksen/ esomeprazol, no documentation was found as to why. Again, this may have been due to contraindications or unawareness of the new protocol.

Despite the new protocol, three patients received preoperative Benzodiazepines. One patient received preoperative Benzodiazepines as part of regular medication. No documentation was found as to why the other two patients received preoperative benzodiazepines. A possible explanation may be anxiety prior to the procedure.

Preoperative bladder emptying was usually controlled but often not documented correctly. The new protocol stated that preoperative bladder emptying should be controlled by the Orthopaedic ward nurse and documented in the anaesthesia record. Usually preoperative bladder emptying was documented by the Orthopaedic ward nurses in the EHR but not in the anaesthesia record. More importantly, preoperative bladder emptying was not documented in six patients. Failure of preoperative bladder emptying increases the risk of postoperative urinary retention, which may lead to increased postoperative morbidity (15, 16).

All patients received thromboembolic prophylaxis according to the new protocol. The incidence of venous thromboembolic disease following elective knee surgery may be as high as 60% without prophylaxis (17). Deep venous thrombosis and pulmonary embolism are both serious adverse effects that may cause readmissions, prolongation of hospital stay and death. Adequate thromboembolic prophylaxis following fast-track primary TKA is therefore paramount.

All patients received spinal anaesthesia according to the new protocol, except for two patients who received general anaesthesia. General anaesthesia is used in fast-track primary TKA when patients refuse spinal anaesthesia or wish to sleep during the procedure. When used for TKA, general anaesthesia is equally effective to and without increased morbidity compared to spinal anaesthesia (18).

Nearly all patients in this study received LIA, but 22 patients received a lower dose than stated by the new protocol. During the study period it was discovered that a second protocol for fast-track primary TKA, used by the surgical nurses, stated a lower LIA dose than the new protocol. If the LIA dose administered by the orthopaedic surgeon(s) was based on the protocol used by the surgical nurses this may explain why most patients received a lower dose of LIA than stated by the new protocol. However, it is unclear if the difference in LIA doses affected the postoperative pain. Irrespectively of this, different protocols concerning the same patients and same procedures should state the same treatment to avoid potential confusion and mistreatment.

Half of the patients in this study did not receive intraoperative dexametasone according to the new protocol. No documentation was found as to why only half of the patients received dexametasone. As stated in the introduction, administration of intraoperative high-dose corticosteroids has shown to reduce postoperative pain and PONV following primary TKA. The fact that half of the patients in this study did not receive dexametasone may have led to increased postoperative pain and PONV.

Close to all patients in this study received tranexamic acid according to the new protocol. Perioperative blood loss and the need for transfusions following primary TKA may lead to increased length of hospital stay (19). Tranexamic acid is a safe, cost-effective method of reducing perioperative blood loss and the need for transfusions (20). As stated in the introduction fast-track surgery aims to reduce length of hospital stay. Therefore, adequate bleeding prophylaxis with tranexamic acid, is important in fast-track primary TKA.

Antibiotic prophylaxis for total joint arthroplasty has shown to be effective (21). In a large Norwegian register study, four doses of iv prophylactic antibiotics on the day of surgery were more effective than fewer doses in primary total hip arthroplasty (22). This may also be true for primary TKA. However, other studies have found a single dose of prophylactic antibiotics to be equally effective compared to multiple doses in hip- and knee arthroplasties (23). Nevertheless, the timing of preoperative prophylactic antibiotics is crucial to ensure that there is an adequate antibiotic concentration in the tissues at surgery (24). Additionally,

in knee arthroplasties prophylactic antibiotics should be finished at least 10 minutes before application of a tourniquet (25). For primary TKA national guidelines strongly recommend antibiotic prophylaxis with cefalotin 2 g iv qds (12). First dose should be given 30-60 minutes before the procedure, second dose 90 minutes after the first dose, then 2 g every 90 minutes up to four doses in total. All patients in this study received four doses of prophylactic antibiotics, except for two patients that did not receive the fourth dose. However, many of the patients received the prophylactic antibiotics at the wrong time according to national guidelines. Especially the last two doses. Failure to provide adequate antibiotic prophylaxis may lead to increased risk of periprosthetic joint infection (PJI). PJI occurs in 1-2% of knee arthroplasties and is the most common cause for revision TKA (26). PJI is a tremendous burden to both patients and health-care institutions (26), and preventing PJI should therefore be of the utmost importance in all arthroplasties, including fast-track primary TKAs.

Postoperative medication was received by nine patients according to the new protocol. A slight improvement when compared to the preoperative medication. In contrary to preoperative paracetamol, close to all patients received postoperative paracetamol according to the new protocol. Yet, only half of the patients received postoperative naproksen/ esomeprazol. Fewer patients received postoperative tapentadol compared to preoperative tapentadol/oksykodonhydroklorid (18 vs 22 patients). No documentation was found as to why 13 and 10 patients respectively did not receive postoperative naproksen/ esomeprazol and tapentadol, except for one patients that did not receive naproksen/ esomeprazol due to allergy. Like for patients that did not receive preoperative naproksen/ esomeprazol and tapentadol/oksykodonhydroklorid, this may have been due to contraindications or unawareness of the new protocol. All patients without contraindications should receive both pre- and postoperative naproksen/ esomeprazol and tapentadol/oksykodonhydroklorid to improve postoperative pain.

An important secondary finding of this study was the lack of documentation regarding patient medication. While collecting data from the EHR it was often difficult to assess the

dosage and timing of the medication. In some cases, it was also difficult to assess which drug that was prescribed. In addition, documentation as to why most patients did not receive medication according to the new protocol was missing. The low level of documentation regarding patient medication is an alarming finding. Lack of documentation has a great potential for harm and should be corrected in the follow-up of this investigation.

4.2 Postoperative pain, PONV and patient satisfaction

The PACU at UNN Tromsø aims to achieve resting pain level (NRS) ≤ 3 for all patients. The median resting pain level in this study was ≤ 3 at arrival PACU, 1 hour postoperative, 2 hours postoperative and discharge PACU, as well as at arrival Orthopaedic ward. However, at evening operation day and postoperative day 1 the median resting pain level had increased to 4. Patients are mobilised following arrival at the Orthopaedic ward which may contribute to increased resting pain. In addition, the intensity of patient surveillance is lower at the Orthopaedic ward compared to the PACU, and this may lead to delayed acknowledge of pain and a delay in treatment with adequate analgesia. Thus, the increase in median resting pain level following arrival at the Orthopaedic ward is not unexpected.

Examination of the data showed that a total of seven patients reported severe pain at one or more assessments. It is unclear why these patients suffered from severe pain and why adequate analgesia was not provided. However, none of the seven patients received premedication according to the new protocol and only two of the patients received postoperative medication according to the new protocol. Additionally, only one of the seven patients received LIA according to the new protocol and only one patient received dexametasone according to the new protocol. All three patients that received preoperative benzodiazepines were among the seven patients that reported severe postoperative pain. It is unclear why these patients received preoperative benzodiazepines, but one possible explanation, as stated in the results, may be anxiety prior to the procedure. Patients with preoperative anxiety are known to have increased risk for postoperative pain (27, 28). This may help explain why the three patients that received preoperative benzodiazepines also suffered from severe postoperative pain in this study. One of the seven patients that

reported severe postoperative pain was also not opioid naïve prior to the procedure. Patients that are opioid tolerant requires significantly higher doses of opioids to treat postoperative pain following TKA (29), and may also experience greater postoperative pain than opioid naïve patients (29).

Previous studies have found mean resting pain levels at 24 hours postoperative ranging from 0,89-5,53 in patients receiving primary TKA with intraoperative administration of LIA (7). Thus, the median resting pain level at 24 hours postoperative in this study does not differ from that found in previous studies. Nevertheless, it is likely to believe that postoperative pain following fast-track primary TKA at UNN Tromsø may be improved with increased adherence to the new protocol.

The worst pain focus was usually located anteromedially by the patients in this study. A proximal FNB can effectively treat anteromedial knee pain (30, 31), but may also cause paralysis of the quadriceps muscles, delay ambulation and increase risk of falling following primary TKA (9). The ideal nerve block following primary TKA should provide effective analgesia and be motor sparing. However, the optimal nerve block for primary TKA is not settled and further research is required (30). Nevertheless, FNB should be considered for anteromedial knee pain following primary TKA when other pain management modalities have failed.

Overall few patients reported PONV. The highest incidence of PONV was reported by six patients at evening operation day and at postoperative day 1. Examination the data showed that a total of 12 patients reported PONV during the study period, but only two patients reported PONV at more than one assessment. This indicates that PONV was treated effectively when occurring in most patients. Three out of the twelve patients that reported PONV vomited. Two out of the three patients that vomited (patient 8 and 15) received general anaesthesia. However, patient 8 and 15 also suffered from severe pain at one or more of the assessments. The incidence of PONV is higher after receiving general anaesthesia compared to regional anaesthesia (32), but may also be higher with increased postoperative pain (33). This is demonstrated by the fact that five of the seven patients that

suffered from severe pain also reported PONV. In addition to the pain itself, patients with severe pain may also receive high doses of postoperative opioids, which has shown to increase PONV in a dose-response relationship (34). Irrespective of cause, PONV is an important clinical outcome to avoid and is often rated worse than postoperative pain by patients (35).

Patient satisfaction following fast-track primary TKA at UNN Tromsø was high. A total of four patients were unsatisfied: two at arrival in the PACU, one at evening operation day and one at postoperative day 1. Examination of the data showed that three out of the four patients reported severe pain at the same assessment as they were unsatisfied. The fourth patient had also experienced severe pain, but prior to the assessment. Additionally, PONV was reported by one of the four patients on the same assessment. During the study period it was not registered why the four patients were unsatisfied. However, it is likely to believe that severe postoperative pain and PONV contributed.

4.3 Strengths and Limitations

This study has several strengths, primarily that it was conducted prospectively. During the five-month study period all patients who received fast-track primary TKA at UNN Tromsø were recruited to the study and included in the analysis. Postoperative pain, PONV and patient satisfaction were assessed objectively in all patients using a specific pain- and satisfactory form. Data was collected from the EHR by two persons in close collaboration (the author and anaesthesiologist Ytrebø) and analysis of all data was done by the same person (the author).

However, this study has also several limitations. The results from this study are entirely observational and no assessments of causality can be made (only hypothesised). Relatively few patients were recruited to this study and the follow-up only lasted 24 hours postoperative. Some of the data concerning postoperative pain, PONV and satisfaction were missing, especially from the assessment at evening operation day. In addition, some of the questions on the pain- and satisfactory form were suboptimal, and adjustments had to be made during analysis. Besides adherence to the new protocol, postoperative pain, PONV and

patient satisfaction no other outcomes or complications were assessed Clear cut-offs to assess adherence/no-adherence to the new protocol were also not established.

4.4 Implications of this study

The results from this study have been presented to the physicians and nurses at the Anaesthesia Department, PACU, Orthopaedic ward and Orthopaedic Department at UNN Tromsø. Hopefully this will increase the adherence to the new protocol and improve the documentation of patient medication. Increased adherence to the new protocol may improve postoperative pain and PONV following fast-track primary TKA at UNN Tromsø. Failure to improve the documentation of patient medication may threaten the patient safety and potentially cause harm.

A new study should be conducted to see if the adherence to the new protocol and the documentation of patient medication were improved following this study. Similar studies should also be conducted for other surgical procedures at UNN Tromsø to evaluate the quality of care and patient safety.

In addition to the implications of this study at UNN Tromsø, the results were also presented at the annual meeting of the Norwegian Society of Anaesthesiology in October 2017.

5 Conclusion

Adherence to the new protocol for fast-track primary TKA at UNN Tromsø was low. Despite low adherence to the new protocol patient satisfaction following fast-track primary TKA at UNN Tromsø was high. Postoperative pain scores and PONV following fast-track primary TKA at UNN Tromsø were acceptable but may be improved with increased adherence to the new protocol.

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7 Tables

Table 1 Demographics

Gender (male/female)	14/14
Age (years)	65 (13)
BMI (kg/m^2)	30,3 (5,1)
ASA-classification (I/II/III)	1/20/7
Knee (left/right)	13/15
Opioid naive	26

Demographics of the 28 patients included in the study. Mean (SD) or number (n). Continuous variables are presented as mean (standard deviation); categorical variables are presented as counts. BMI, body mass index; ASA, American Society of Anesthesiologists; Opioid naive, patient not using any opioids upon hospitalization.

Table 2 Adherence to preoperative measures

Premedication according to protocol? (yes/no)	3/25
Preoperative paracetamol according to protocol? (yes/too low dose/no)	6/20/2
Preoperative naproksen 500 mg/ esomeprazol 20 mg according to protocol? (yes/no)	15/13*
Preoperative tapentadol 50 mg or oksykodonhydroklorid 10 mg (>70 years) according to protocol? (yes/no)	22/6
No preoperative benzodiazepines according to protocol? (yes/no)	25/3†
Preoperative bladder emptying controlled and correctly documented according to protocol?	6/16/6

(yes/not correctly documented/no)	

Adherence to the preoperative measures stated by the new protocol. *One patient did not receive naproksen/ esomeprazole due to allergy. †One patient received benzodiazepine as part of regular medication.

Table 3 Adherence to intraoperative measures

Spinal anaesthesia according to protocol? (yes/general anaesthesia)	26/2
LIA according to protocol? (yes/wrong dose/unknown dose)	4/22/2
Dexametasone according to protocol? (yes/wrong dose/no)	10/4/14
First dose of tranexamic acid according to protocol? (yes/no)	28/0
Second dose of tranexamic acid according to protocol? (yes/wrong timing)	26/2

Adherence to the intraoperative measures stated by the new protocol. LIA, local infiltration analgesia.

Table 4 Adherence to antibiotic prophylaxis

PA first dose (yes/wrong timing)	20/8
PA second dose (yes/wrong timing)	23/5
PA third dose (yes/wrong timing/wrong dose)	5/21/1

PA fourth dose (yes/wrong timing/wrong dose/no)	5/20/1/2

Adherence to prophylactic antibiotics stated by the new protocol and national guidelines. PA, prophylactic antibiotics.

Table 5 Adherence to postoperative measures

Postoperative medication according to protocol? (yes/no)	9/19
Postoperative paracetamol according to protocol? (yes/wrong dose/wrong timing)	26/1/1
Naproksen 500 mg, esomeprazol 20 mg according to protocol? (yes/no)	15/13*
Tapentadol 50 mg according to protocol? (yes/no)	18/10

Adherence to postoperative measures stated by the new protocol. *One patient did not receive naproksen 500 mg/ esomeprazole 20 mg due to allergy.

Table 6 Postoperative nausea and vomiting (yes/no/missing)

Arrival PACU	0/28/0
1-hour postoperative	3/25/0
2-hours postoperative	1/26/0
Discharge PACU	2/22/0
Arrival Orthopaedic Ward	2/23/3
Evening operation day	6/14/8
Postoperative day 1	6/22/0

Postoperative nausea and vomiting reported by the patients in the study. Yes, nausea/vomiting now or since last assessment; no, no nausea/vomiting now or since last assessment. Missing, patient data not registered.

Table 7 Patient satisfaction (satisfied/unsatisfied/missing)

Arrival PACU	24/2/2
1-hour postoperative	26/0/2
2-hours postoperative	25/0/3
Discharge PACU	23/0/5
Arrival Orthopaedic Ward	25/0/3
Evening operation day	14/1/13
Postoperative day 1	27/1/0

Satisfaction level reported by the patients in the study. Missing, patient data not registered.

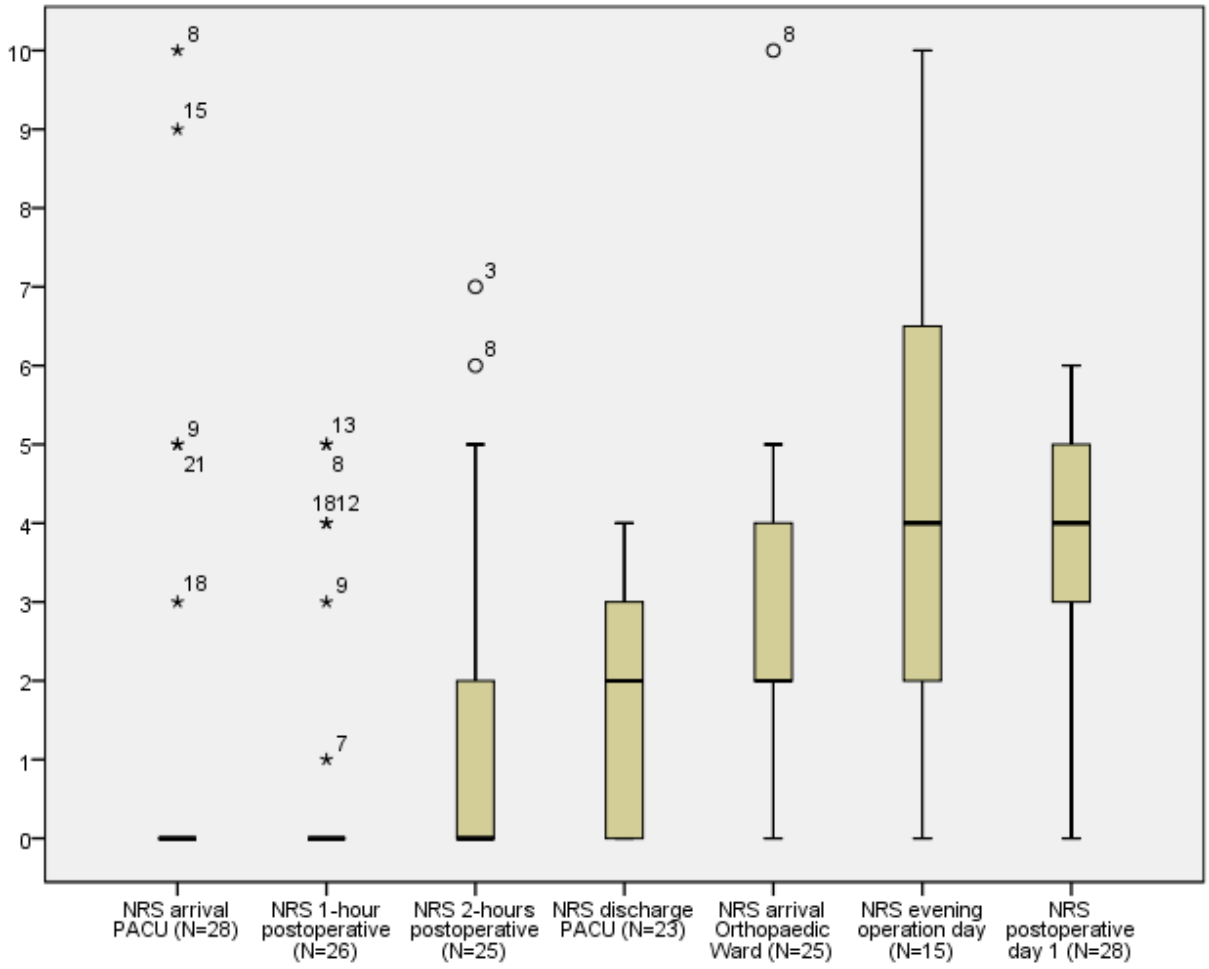
Table 8 Locations of the worst pain focus (anteromedial/posterior/other/none/missing)

Arrival PACU	4/0/1/23/0
1-hour postoperative	4/0/2/21/1
2-hours postoperative	5/0/3/15/5
Discharge PACU	13/0/3/6/6
Arrival Orthopaedic Ward	13/1/5/6/3
Evening operation day	8/1/4/1/14
Postoperative day 1	18/4/6/0/0

Locations of the worst pain focus reported by the patients in the study. Missing, patient data not registered.

8 Figures

Figure 1 Postoperative resting pain



Postoperative resting pain at seven points during the first 24 hours postoperative. Data is shown as a box-plot with ranges (whiskers), interquartile ranges (boxes), medians (solid lines) and outliers (circles or stars). Outliers represented as circles are cases with values between 1.5 and 3 box lengths from the upper or lower edge of the box. Outliers represented as stars are cases with values above 3 box lengths from the upper or lower edge of the box. NRS, numeric rating scale; N, number of patients.

9 Appendices

- **Appendix A:** The new anaesthesia protocol containing LIA for fast-track primary TKA at UNN Tromsø implemented in January 2017.
- **Appendix B:** The pain- and satisfaction form used to collect patient data in the study.
- **Appendix C: S**tudy approval from Data protection officer at UNN Tromsø
- **Appendix D:** GRADE 1
- **Appendix E:** GRADE 2
- **Appendix F:** GRADE 3
- **Appendix G:** GRADE 4
- **Appendix H:** GRADE 5

Dokumentansvarlig: Solveig Fagerholt
Dokumentnummer: PR9175
Godkjent av: Tanja Lise Sollberger
Versjon: 8.2
Gyldig for: Innslusa Tromsø UNN; NevOrt UNN

Anestesi ved Fasttrack Kneprotese

Hensikt/Omfang

Retningslinjen skal sikre at pasienter som får anestesi ved Fasttrack kneproteser får sikker behandling og et godt postoperativt resultat.
Denne prosedyren gjelder ikke bytte av proteser der det er forventet lang operasjonstid, større kirurgi eller infiserte proteser.

Grunnlagsinformasjon

Ved Fasttrack protese kirurgi er hovedmål en pasient som kan mobiliseres tidlig. Pasienter skal ut av sengen og stå på operert ben operasjonsdagen.

LCS- kneprotese:
Til alle som trenger kneprotese pga:
- Primær artrose
- Sekundær artrose etter ulike skader
- Reumatoid artrittpasienter

Operasjonstid: Primærproteser ca 1,5 timer.

Arbeidsbeskrivelse

Ansvar
Sykepleiere og leger v/anestesi, oppvåkning og Ortopedisk døgnenhet.

Preoperativt

Inkluderte: Alle. Pasienten tilses på Kneskole i henhold til avdelingens rutiner. ASA III må vurderes individuelt iht grunnsykdom (3,4,6)

Eksklusjon*:* Ingen. Komplekse kroniske smertepasienter som LAR pasient skal vurderes individuelt.

Tromboseprofylakse forordnes av ortoped etter gjeldende retningslinjer PR13776 Tromboseprofylakse (Fragmin)- Ortopedi- og plastikkirurgisk avdeling (ORPL) UNN.

Pre-, per- og postoperativ antibiotika: Forordnes av ortoped etter gjeldende retningslinjer(5).

Premedikasjon: Gis på sengepost etter gjeldende prosedyre. Forordnes av ortoped (1, 4).

Paracetamol tbl 1g til pasient <70kg og 2g til pasient >70kg
Vimovo 1tbl, 500 mg/20mg (Naproxen/ Esompreazol)
Palexia depot tbl 50 mg (μ-opioid) per os gis rutinemessig etter gjeldende retningslinjer såfremt det ikke foreligger sterke kontraindikasjoner**.** Alternativ til eldre>70 år: OxyContin tbl 10mg
Benzodiazepiner **gis ikke**. .

Blæretømming pre.opr: Ansvarlig sykepleier ved sengepost tilser at pasienten tømmer urinblæren like før overflytting til operasjonsenhet og dokumenterer tidspunkt på anestesiskjema. PR40983 «Overfylt urinblære-observasjoner og tiltak i perioperativ fase»

Peroperativt

Forberedelse av pasienten og bedøvelse foregår vanligvis på innledningsrom og fullføres på operasjonsstuen.

Utstyr/ monitorering: Venekanyle, O2 på nesekateter, EKG-monitorering, pulsoxymetri,
non-invasiv (evt invasiv BT-måling),Tempmåling(øre), varmluftslaken

Anestesimetode: Som hovedregel velges regionalanestesi. Spinal er førstevalget.
Marcain (bupivacaine) 0.5% plain, helst i nivå L2-3.
Viktig! Pasienten skal være totalt avslappet i beinet, for at operatøren skal kunne beregne ligamentbalansen

Leiring: Rygg

Blodtomhet: Per.opr.

Antibiotica: (5)**:** Cefalotin 2g x 4 iv
1.dose:30-60min før kirurgi.
2.dose: (ca.90min etter 1.dose) avtal 2.dose med kirurg pga blodtomhet

Fibrinolysehemmer: Traneksamsyre 10mg/kg
1.dose gis 15min før blodtomhet slippes opp. Ortoped gir beskjed!
2.dose gis 3timer etter 1.dose.
Traneksamsyre gis såfremt det ikke foreligger kontraindikasjoner. Ordineres av ortoped.
Prosedyre PR30319 Cyklokapron ved protesekirurgi

Dexametason: 16 mg iv

Sementering:
Tibiadel med sement og Femurdel uten eller med sement.
Roterende plattform av plast mellom femur og tibia muliggjør anatomisk bevegelse i kneledd.
Når sementering begynner starter vi klokka. Første 3 minutt beskjed hvert 30. sekund.
Så hvert minutt til 10 min.

Lokalanestesi: Ropivakain 2 mg/ml 120-150 ml tilsatt Adrenalin settes av ortoped under lukning av sår.

Blærescanning og evt.engangskateterisering:
Vi følger prosedyre **PR40983** «Overfylt urinblære-observasjoner og tiltak i perioperativ fase»

Postoperativt

Væske: Rest Ringer Acetat

Smertelindring: (forordnes av lege):
Paracetamol tbl. 1 eller 1,5g x 4
Vimovo tbl. 500mg/20mg x 2
Palexia depot tbl. 50mg x 2
Morfin iv v/behov
OxyNorm 5 mg v/behov på sengepost.

Studier viser at denne smertelindring fungerer for over 90% av pasienter. For pasienter som ikke kan få NSAIDS eller som har stor, uforventet smerte vil andre løsninger være indisert, f.eks. nerveblokade, epidural, PCA eller andre opioider.

Prøver: Hb-ktr. og evt andre prøver vurderes i hvert enkelt tilfelle.

Referanser:

1. *Anestesiologisk metode Fast-track hofte- og kneprotese Ortopedisk avdeling, St.Olavs Hospital, Trondheim.*
2. *Miller (kap 61; Anesthesia for Orthopedic Surgery).*
3. *Avdelingens praksis*
4. *Ortopedisk avdelings praksis.*
5. *Antibiotika i sykehus. Nasjonal faglig retningslinje for bruk av antibiotika i sykehus(Helsedirektoratat)*
6. *ASA* klassifikasjonstabell for UNN Tromsø(Intranett- Faglig)*

APPENDIX B:

Postoperativ smerte hos pasienter som har fått innsatt total kneprotese

Skjemaet følger pasientkurven. **Pasient id(navnelapp):**

	Ankomst på oppvåkningen	1 t	2 t	Utskrivning fra oppvåkningen	Ankomst på sengeposten	Kveld opr dagen (ca 8 t postopr)	Postopr dag 1 (ca 24 t postopr)
Klokkeslett							
Smertegrad nå (NRS 0-10)							
Maks grad av smerte i ro siden sist måling (NRS 0-10)							
Minste grad av smerte i ro siden sist måling (NRS 0-10)							
Gjennomsnittlig smerte i ro siden sist måling (NRS 0-10)							
Det sterkeste smertefokuset i kneet nå (ant/med/lat/post/globalt)							
Kvalme nå/siden sist (ja/nei)							
Oppkast nå/siden sist (ja/nei)							
Pasienttilfredshet nå (en av de fem kategoriene under): **-Svært fornøyd (1)** **-Meget fornøyd (2)** **-Fornøyd (3)** **-Misfornøyd (4)** **-Svært misfornøyd (5)**							

Ved spørsmål, vennligst kontakt stud.med. Arnstein Berg tlf. 93442740 eller professor Lars Marius Ytrebø tlf. 90788058

Eventuelle kommentarer/begrunnelser fra behandlere	
Eventuelle kommentarer/begrunnelser fra pasient	

Ved spørsmål, vennligst kontakt stud.med. Arnstein Berg tlf. 93442740 eller professor Lars Marius Ytrebø tlf. 90788058

APPENDIX C:

UNIVERSITETSSYKEHUSET NORD-NORGE
DAVVI-NORGGA UNIVERSITEHTABUOHCCEVIESSU

PERSONVERNOMBUD

Til
Lars Marius Ytrebø
Anestesi- og operasjonsavdelingen

Deres ref.:	Vår ref.:	Saksbehandler/dir.tlf.:	Dato:
	2017/877	Kristin Andersen/77626506	6.2.2017

GODKJENNING AV BEHANDLING AV PERSONOPPLYSNINGER

Det vises til Meldeskjema for forskningsstudier, kvalitetsstudier og annen aktivitet som medfører behandling av personopplysninger som er melde- eller konsesjonspliktig i henhold til helseregisterloven og personopplysningsloven med forskrifter, mottatt 19.12.2016

Meldingen gjelder prosjektet/registeret:

> ***Nr.*** ***0649***
> ***Navn på prosjektet:*** *Anesthetic techniques and postoperative analgesia methods for total knee arthroplasty*

Prosjektet er en ***kvalitetsstudie*** hvor Universitetssykehuset Nord-Norge HF er behandlingsansvarlig.

> ***Formål:*** *«Kvalitetsforbedrende arbeid innenfor feltet smerte og perifere nerveblokader»*

Personvernombudet (PVO) har vurdert prosjektet, og finner at behandlingen av personopplysningene vil være regulert av § 7-12 i Personopplysningsforskriften og hjemlet etter Helsepersonelloven § 26.

PVO forutsetter at prosjektet gjennomføres i tråd med de opplysningene som er gitt, samt i henhold til Personopplysningsloven og Helseregisterloven med forskrifter. Videre forutsettes det at data anonymiseres etter prosjektavslutning ved at kodelista slettes.

PVO har på bakgrunn av og tilsendte meldeskjema med vedlegg registrert prosjektet og opprettet et eget område (mappe) på \\hn.helsenord.no\UNN-avdelinger\felles.avd\forskning (o:\) med navn **0649** hvor all data i forbindelse med prosjektet skal lagres.
I tillegg er det opprettet et område på \\hn.helsenord.no\UNN-avdelinger\felles.avd\forskning\key med navn **0649N** hvor nøkkelfil skal oppbevares. Tilgang til dette området er begrenset til kun å omfatte prosjektleder og den som prosjektleder definerer. PVO vil ha tilgang til området.

PVO gjør oppmerksom på at dersom registeret skal brukes til annet formål enn det som er nevnt i meldingen, må dette meldes særskilt.

PVO skal ha melding når registeret er slettet. PVO skal også ha melding dersom registeret ikke er slettet eller ikke ferdig behandlet innen 3 år.

Med vennlig hilsen

UNIVERSITETSSYKEHUSET NORD-NORGE HF

PVO-Teamet
e.f.

Kopi: Klinikksjef Eva-Hanne Hansen

APPENDIX D:

Reference: Andersen LO, Husted H, Otte KS, et al. High-volume infiltration analgesia in total knee arthroplasty: a randomized, double-blind, placebo-controlled trial. Acta anaesthesiologica Scandinavica 2008; 52: 1331-5.

Design: RCT	
Level of documentation:	Ib
GRADE:	⊕⊕⊕⊕

Objective	Methods and materials	Results	Discussion/ comments
Evaluate the analgesic effect of high-volume infiltration analgesia in bilateral total knee arthroplasty. **Conclusion** High-volume infiltration analgesia is effective in knee arthroplasty and, due to its simplicity, may be preferable compared with other analgesic techniques in knee arthroplasty. **Country** Denmark **Year of data collection** October 2006 to April 2007	Twelve consecutive patients scheduled for total bilateral knee arthroplasty were included from October 2006 to April 2007. Inclusion criteria: consecutive patients scheduled for total bilateral knee arthroplasty, able to understand and speak Danish and able to give informed oral and written consent to participate. Exclusion criteria: treatment with opioids or steroids, rheumatoid arthritis or other immunological diseases, a history of stroke or any neurological or psychiatric disease potentially influencing pain perception, allergies to any of the drugs administered and a body mass index >40. Intervention: infiltration with 170 ml ropivacaine (0.2%) and epinephrine (10 µg/ml) in one knee, and similar infiltration with 170 ml of 0.9% saline in the opposite knee. Postoperative injection of the drug mixture [40 mg ropivacaine and epinephrine (10 µg/ml)] or 0.9% saline was administered intra-articulary through the catheters placed during surgery in accordance with the randomization. All patients received PCA and the same multimodal pain management regime postoperatively. All inclusion and data registration were performed by one investigator. All anaesthetic procedures were performed by one of two anaesthesiologists and all patients were operated by one of two surgeons. Allocation of which knee was to receive active treatment was determined by randomization, using a computer-generated random sequence and opaque sealed envelopes. To ensure complete blinding of the patients, the surgeon and the investigator recording post-operative pain data, the randomization was not revealed until completion of the entire study. The medicine used for each individual patient was prepared by one investigator not otherwise involved in patient data collection. The primary end-point was to compare post-operative pain in each leg, which was assessed using a Numeric Rank Scale (NRS) from 0 to 10, at rest, upon 45° flexion of the knee and with the leg straight and 45° elevated. Pain was recorded at 4, 8, 9, 24, 24.5, 25, 26, 32 and 48 h post-operatively. Throughout the 48-h study period, the amount of morphine delivered via the PCA pump as well as the length of hospital stay were registered. All patients were discharged directly to their homes and discharge criteria were functional: ability to get in and out of bed, get dressed, get into and up from a chair, ability to walk independently for 50 m with appropriate walking aids and acceptance of discharge. The number of participants was arbitrarily set to 12, because no meaningful power calculation could be performed from previously published data in unilateral knee replacement. Tests for significant differences between treatment groups were performed using the Wilcoxon signed ranks test. P values <0.05 were considered statistically significant. All data analysis was performed using SPSS for windows, ver. 12.0 (SPSS Inc., Chicago, IL).	Twelve consecutive patients were included because no patients refused to participate. Patient characteristics were seven men/five women, mean age 69 years (range 57–87), mean weight 85 kg (range 67–101), mean body mass index 29 (range 25–36) and American Society of Anesthesiologists Physical Status I/II/III=3/8/1. NRS pain scores were significantly lower from the knee infiltrated with ropivacaine and epinephrine compared with the knee infiltrated with saline. This reduction in NRS pain scores was significant from 4 to 25 h post-operatively at rest, from 4 to 32 h post-operatively upon 45° flexion of the knee and from 4 to 26 h post-operatively when the leg was straight and 45° elevated. In the PACU, [median (interquartile range)] iv administration of morphine was 20 mg (0–75 mg) and cumulated post-operative PCA morphine administration [median (interquartile range)] was 8 mg (4–14), 19 mg (9–32), 35 mg (22–56), 48 mg (26–70) and 58 mg (33–86) at 4, 8, 24, 32 and 48 h post-operatively. The mean duration of surgery was 109 min (range 64–150). Hospital stay (median) was 4 days (range 3–19). A detailed description of study side effects was not performed, but no major side effects, including cardiac and hemodynamic changes requiring treatment, were observed in the study period (intraoperatively and 0–48 h post-operatively).	**Checklist:** -Did the trial address a clear question? Yes -Was the assignment of patients to treatments randomised? Yes -Were all patients who entered the trial properly accounted for at its conclusion? Yes -Were patients, health workers and study personnel 'blind' to treatment? Yes -Were the groups similar at the start of the trial? Yes (patients served as their own controls) -Aside from the experimental intervention, were the groups treated equally? Yes -How large was the treatment effect? Significant differences in median NRS ranged between 1 and 6 -How precise are the estimates of the treatment effect? Significant differences were either P<0,05 or P<0,01 -Can the results be applied to the local population? Yes -Were all clinically important outcomes considered? Yes -Are the benefits worth the harms and costs? Yes **Strengths:** Patients served as their own controls. **Limitations:** Morphine requirements could not be assessed due to the study design.

APPENDIX E:

Reference: Busch CA, Shore BJ, Bhandari R, et al. Efficacy of periarticular multimodal drug injection in total knee arthroplasty. A randomized trial. The Journal of bone and joint surgery American volume 2006; 88: 959-63.

Design: RCT	
Level of documentation:	Ib
GRADE:	⊕⊕◯◯

Objective	**Methods and materials**	**Results**	**Discussion/ comments**
Investigate the use of a periarticular injection of multimodal drugs, consisting of an opioid (epimorphine), a nonsteroidal anti-inflammatory drug (ketorolac), a long-acting local anaesthetic (ropivacaine), and epinephrine, to provide analgesia following total knee arthroplasty. **Conclusion** Intraoperative periarticular injection with multimodal drugs can significantly reduce the requirements for patient-controlled analgesia and improve patient satisfaction, with no apparent risks, following total knee arthroplasty. **Country** Canada **Year of data collection** Unclear	64 patients undergoing unilateral TKA were randomized with the use of randomization tables. 32 patients received an intraoperative periarticular injection of analgesic drugs, and 32 patients did not. Inclusion criteria: age < 80 years, weight 50-120 kg, and an ability to provide informed consent for, and cooperate with, the study. Exclusion criteria: major psychological problems, previous drug dependency, allergies to any of the ingredients of the injection, renal insufficiency, abnormal liver enzymes, a history of stroke or a major neurological deficit, or uncontrolled angina and bifascicular blocks with prolonged QT intervals. The knee arthroplasty was performed through a standard medial parapatellar approach. The injection contained 400 mg of ropivacaine, 30 mg of Toradol (ketorolac), 5 mg of epimorphine, and 0.6 mL of epinephrine (1:1000). These were mixed with sterile normal saline solution to make up a combined volume of 100 mL in the operating room. Operative anaesthesia was either general or regional. The anaesthetic regimen was standardized. Five patients had blood samples taken at thirty minutes, one hour, and four hours postoperatively to measure venous blood (proteinbound) ropivacaine levels. All patients received PCA for 24 hours after the surgery. The consumption of PCA was measured at different time-points during the 24 postoperative period and the patient's overall analgesic consumption was measured and converted to morphine equivalents to allow for comparison of the two treatment groups. Patients used VAS to assess pain, both at rest and during activity, as well as their satisfaction in the preoperative assessment clinic (two to three weeks prior to the surgery), on the day of the surgery, in the PACU, during the inpatient stay, and finally at the six-week follow-up examination. The VAS for pain and satisfaction ranged from 0 mm (indicating no pain or completely dissatisfied) to 100 mm (indicating extreme pain or completely satisfied) in 10-mm increments. Specific note was made of any signs of cardiac or central nervous system toxicity or wound complications. Knee Society clinical rating scores13 and scores according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)14 were collected prospectively for all patients. All patients had an ultrasound study of the lower limb to screen for deep vein thrombosis at five days after the surgery. Statistical analysis of the data set was performed with use of the Kolmogorov-Smirnov test ($p < 0.05$) for normality and subsequently a normal t test. The analyses were performed with SPSS software (version 11.5; SPSS, Chicago, Illinois).	Patients who had received the multimodal drug infiltration used significantly less patient-controlled analgesia at six hours ($p < 0.01$) and at twelve hours ($p = 0.016$) and had a significantly lower overall requirement for patient-controlled analgesia over the first twenty-four hours after surgery ($p < 0.001$) compared with the patients who had received no infiltration. There was no difference in the overall analgesic consumption in morphine equivalents between the two patient groups. The group that had had the infiltration had significantly greater mean VAS for patient satisfaction in the PACU ($p = 0.016$) and four hours postoperatively ($p = 0.013$) and significantly lower VAS for pain during activity in the PACU ($p = 0.04$) and at four hours after the surgery ($p = 0.007$). There was no difference between treatment groups regarding the numbers of patients receiving general or spinal anaesthesia ($p = 0.446$). At six weeks, no significant difference in the range of motion could be detected between the two groups. In addition, with the numbers available, there was no significant difference in the average hospital stay or the rate of wound complications between the two groups. One patient who had received the infiltration had a deep vein thrombosis postoperatively. The maximum level of unbound ropivacaine observed was 60 ng/mL, which is 2.5 times below the toxic level (150 ng/mL).	**Checklist:** -Did the trial address a clear question? yes -Was the assignment of patients to treatments randomised? yes -Were all patients who entered the trial properly accounted for at its conclusion? yes -Were patients, health workers and study personnel 'blind' to treatment? No, only patients were blinded -Were the groups similar at the start of the trial? yes -Aside from the experimental intervention, were the groups treated equally? yes -How large was the treatment effect? Ranging between 0-20 mm VAS. -How precise are the estimates of the treatment effect? See the results -Can the results be applied to the local population? yes -Were all clinically important outcomes considered? yes -Are the benefits worth the harms and costs? yes **Limitations:** Only patients were blinded. Anaesthesia technique was not standardized. No systemic multimodal analgesic regime was used.

APPENDIX F:

Reference: Fan L, Yu X, Zan P, et al. Comparison of Local Infiltration Analgesia With Femoral Nerve Block for Total Knee Arthroplasty: A Prospective, Randomized Clinical Trial. The Journal of arthroplasty 2016; 31: 1361-5.

Design: RCT	
Level of documentation:	Ib
GRADE:	⊕⊕⊕○

Objective	**Methods and materials**	**Results**	**Discussion/ comments**
Evaluate the effect of single shot LIA for postoperative analgesia and functional outcomes after TKA by comparing with single shot FNB. **Conclusion** No significant differences were observed between the 2 treatment groups. LIA could provide a similar analgesic effect to FNBs with a low incidence of complications. **Country** China **Year of data collection** May 2012 to September 2014	Prospective, patient- and assessor-blinded, single-center randomized controlled trial. Included: all patients scheduled to undergo primary TKA at Shanghai Tenth People's Hospital from May 2012 to September 2014. Excluded: patients with known allergies to any of the test drugs, those with major systemic illnesses, chronic users of opioids or NSAIDS, a history of deep vein thrombosis, and previous knee surgery. A total of 183 patients were eligible for the study, and 23 patients were excluded based on the exclusion criteria. Then 160 eligible patients undergoing TKA were prospectively randomized to 1 of 2 study arms using sealed, opaque envelopes that were opened before surgery. Interventions: FNB was performed preoperatively: 20mL of ropivacaine 0.5% in group A (FNB) and normal saline in group B (LIA). Two experienced anaesthesiologists performed the nerve block and were not blinded to the treatment allocation. After cementing the prostheses, 50 mL of cocktail mixture containing morphine (1 mL: 10 mg), ropivacaine (10 mL: 100 mg), and diprospan (1 mL: 5 mg betamethasone dipropionate and 2 mg betamethasone sodium phosphate) was injected into the periarticular soft tissue in group B. In group A, cocktail was replaced by normal saline. The LIA procedure was conducted by 2 chief surgeons who were not blinded. After surgery, all patients received PCA and equal fluid- and pain management. Outcomes measurement: morphine consumption of the PCA, VAS at rest and with movement, Knee Society Score (KSS) and ROM before and after surgery, inpatient days, complications (including nausea and vomiting, urinary retention, infection, deep venous thrombosis, hematoma, and nerve injury) were collected and analysed. Data Analysis: Statistical analysis was performed with SPSS statistical software 20.0. The results were presented as the mean ± standard deviation. Student's t test was used for normally distributed parameters, and the chi-square test was used for proportional data. A P value <0.05 was regarded as statistically significance.	A total of 160 patients were successfully recruited and 3 patients were withdrawn after protocol violation. There was one patient in each group who received spinal rather than general anaesthesia, and one patient who was randomized to the group A failed to complete the follow-up. Finally, there were 78 patients in group A and 79 patients in group B. Patient demographics and surgery details showed no statistical difference between 2 groups. There was no significant difference between 2 groups with respect to the daily and the cumulative morphine consumption of PCA. As to the pain scores, the local infiltration group (group B) had less pain as measured with the VAS during the first 24 hours only (7.1 of 0.6 vs 6.9 of 0.5, P = .01), compared with group B. Thereafter, no significant difference was observed between the 2 groups. The ROM, KSS, and length of stay showed no significant differences. Eighteen patients in group A and 21 patients in group B experienced mild-to-medium nausea or vomiting, and 10 patients in group A and 15 patients in group B were given metoclopramide 5-10 mg during the study. No urinary retention case was seen during inpatient days. One patient in group B had dizziness, and no special treatment was given. One patient in group A got femoral nerve injury and her quadriceps power dropped to level 2, which was recovered to level 5 after 45 days rehabilitation training. Each group had one case of deep venous thrombosis, and patients were given thrombolytic anticoagulant therapies. In both groups, there was neither prolonged wound discharge nor deep surgical site infection.	**Checklist:** -Did the trial address a clear question? Yes -Was the assignment of patients to treatments randomised? Yes -Were all patients who entered the trial properly accounted for at its conclusion? Yes -Were patients, health workers and study personnel 'blind' to treatment? No, but patients and assessors were blinded. -Were the groups similar at the start of the trial? Yes -Aside from the experimental intervention, were the groups treated equally? Yes -How large was the treatment effect? The local infiltration group had less pain measured with the VAS during the first 24 hours (7.1 of 0.6 vs 6.9 of 0.5, P = .01), -How precise are the estimates of the treatment effect? See the previous question -Can the results be applied to the local population? Yes -Were all clinically important outcomes considered? Yes -Are the benefits worth the harms and costs? Yes **Limitations** The morphine use after surgery does not represent the tendency of analgesia used today, which is to avoid morphine pumps and to use other modalities.

APPENDIX G:

Reference: Roberts GW, Bekker TB, Carlsen HH, et al. Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. Anesthesia and analgesia 2005; 101: 1343-8.

Design: Prospective cohort study	
Level of documentation:	IIb
GRADE:	⊕⊕⊕○

Objective	Methods and materials	Results	Discussion/ comments
Examine the effect of known risk factors for POV, with a focus on the relationship between vomiting and opioid use in the 48 h postoperatively. **Conclusion** There is a strong relationship between the amount of postoperative opioid used and POV. The accuracy of various risk scoring approaches may have been undermined by not allowing for this relationship. Patients likely to have larger postoperative opioid requirements should be priority targets for opioid reduction or vomiting prevention strategies. **Country** Australia **Year of data collection** Unclear	All patients receiving surgical procedures requiring anaesthesia (excluding local anaesthesia) with an expected length of stay of ≥2 days who did not receive perioperative antiemetic prophylaxis were eligible. The approach to analgesia for any given patient was at the discretion of the anaesthesiologist. Those patients not using epidural analgesia or PCA were given pain relief with a combination of IV and oral medication, on an "as required" basis. Patients already receiving drugs with antiemetic properties, including corticosteroids, were excluded. An episode of POV was defined as vomiting or retching over any 2-min period. The severity or duration of nausea was not recorded, only if it was present or not, as determined by the patient. Patients who vomited were automatically included as having experienced nausea at that point. Patients routinely received postoperative rescue antiemetics if they vomited, or experienced ≥10 min of debilitating nausea. In the first instance, they received 10 mg of IV metoclopramide, followed 10 min later by 4 mg of IV ondansetron if the nausea and vomiting were still not controlled. Nausea and vomiting episodes were recorded 0.5, 1, 2, 4, 8, 12, 24, and 48 h postoperatively. Opioid doses, both intra- and postoperative, were recorded for the 0- to 24-h and 24- to 48-h periods postoperatively. All opioid doses, regardless of route of administration or type of opioid, were converted to the equianalgesic dose of IV morphine for comparative purposes. These values were predetermined on current available literature and the clinical expertise of the participating anaesthesiologists. Fentanyl was used for all epidurals and was considered equipotent via epidural or IV route. One milligram of IV morphine was considered to be equianalgesic with 10 g of spinal morphine. Parametric data were compared using a Student's t-test. Kaplan-Meier plots were used to examine the incidence of POV over time. Cox regression analysis was used to examine variables influencing POV. The significance level was set at 5%.	Data were collected on 193 patients. In the first 24 h postoperatively, 23.8% of patients experienced POV and a further 27.5% experienced PON with no associated vomiting. In the 24- to 48-h postoperative period, 6.5% of patients vomited and a further 23.2% experienced nausea only. Cox regression analysis included gender, history of POV or motion sickness, smoking, duration of anaesthesia, age, and opioid dose, and revealed only opioid use (P = 0.025) and female gender (P = 0.038) as factors influencing POV. Use of PCA or epidural analgesia were markers for large-dose opioid use in the first 24 h (91.5 and 83.2 mg of morphine or equivalent for PCA and epidural analgesia, respectively, versus 17.5 mg for non-users, P 0.001). This was associated with more frequent POV and PON. Patients not using PCA or epidural analgesia experienced less POV and PON (P 0.001 for both). Those patients who experienced POV and PON in the 24- to 48-h period postoperatively had significantly larger opioid use during this period than those who did not (P 0.01 for both). Patients were divided into quartiles according to opioid dose to further examine the relationship between opioid dose and POV in the first 24 h postoperatively. There was a strong logarithmic dose-response relationship with POV (r^2 = 0.98, P < 0.01), as well as PON (r^2 = 0.98, P = 0.01). When patients receiving opioids via the spinal or epidural route were removed from analysis, this relationship remained largely intact, although the dose-response relationship with POV in this subgroup was better suited to a linear relationship (r^2 = 0.99, P 0.01 for linear, r^2 = 0.82, P = 0.09 for logarithmic, n = 145). PON remained best correlated to a logarithmic relationship (r^2 = 0.99, P < 0.01 for logarithmic versus r^2 = 0.88, P = 0.07 for linear).	**Checklist:** -Did the study address a clearly focused issue? Yes -Was the cohort recruited in an acceptable way? Unclear -Was the exposure accurately measured to minimise bias? Yes -Was the outcome accurately measured to minimise bias? Yes - Have the authors identified all important confounding factors? Unclear -Have the authors taken account of the potential confounding factors in the design and/or in their analysis? Yes -Was the follow up of subjects complete enough? Yes -Was the follow up of subjects long enough? Yes -How large was the treatment effect? Large, dose-response relationship -How precise was the estimate of the treatment effect? Precise, see the results -Do you believe the results? Yes -Can the results be applied to the local population? Yes -Do the results of this study fit with other available evidence? Yes -What are the implications of this study for practice? Reduce the use of opioids for postoperative pain management to avoid PONV (or use adequate prophylaxis in risk patients). **Limitations** Relative few patients.

APPENDIX H:

Reference: Essving P, Axelsson K, Kjellberg J, et al. Reduced morphine consumption and pain intensity with local infiltration analgesia (LIA) following total knee arthroplasty: A randomized double-blind study involving 48 patients. Acta orthopaedica 2010; 81: 354-60

Design: RCT	
Level of documentation:	Ib
GRADE:	⊕⊕⊕⊕

Objective	Methods and materials	Results	Discussion/ comments
Evaluate if LIA reduces morphine consumption during the first 48 postoperative hours following TKA. Secondary endpoints: pain intensity, time to home readiness, side effects, plasma concentrations of LA, knee function, and patient satisfaction. **Conclusion** LIA provides excellent pain relief and lower morphine consumption following TKA, resulting in shorter time to home readiness and higher patient satisfaction. There were few side effects and systemic LA concentrations were low. **Country** Sweden **Year data collection** From April 2007 through September 2008.	78 consecutive TKAs because of osteoarthritis were screened for eligibility. Inclusion criteria: age 20–85 years, ASA I–III, and normal preoperative mobility. Exclusion criteria: known allergy or intolerance to one of the study drugs, serious liver-, heart- or renal disease, inflammatory joint disease, chronic pain, or any bleeding disorder. 30 patients were excluded prior to randomization due to exclusion criteria. Patients were randomised into 2 groups with 24 patients in each, using computer-generated randomized numbers. The patients, the 2 study investigators, the study physiotherapist, and all the staff concerned with the postoperative care of the patients were blinded to the group randomization. All patients received general anaesthesia. In group A, 400 mg ropivacaine, 30 mg ketorolac, and 0.5 mg epinephrine (total volume 166 mL) were infiltrated by the surgeon into the soft tissues periarticularly during the operation. Group B received no intraoperative injection. After 21 h, 200 mg ropivacaine, 30 mg ketorolac, and 0.1 mg epinephrine in total volume of 22 mL were injected intraarticularly in group A and a similar volume of saline was injected in group P. All patients received the same postoperative pain medication. CA-morphine consumption was recorded during 0–24, 24–48, and 0–48 h postoperatively. Oral analgesic consumption was recorded during 0–24, 24–48, and 0–48 h. Total analgesic consumption 0–48 h postoperatively was calculated using equivalent dose of intravenous morphine. Pain assessment (VAS) was made preoperatively and at 3, 6, 12, 21, 22 (i.e. 1 h after test drug injection), 27, and 48 h, and also on days 3 and 14, and at 3 months postoperatively. Pain was assessed both at rest and on flexion of the knee by 60 degrees. The time to fulfillment of discharge criteria (home readiness) was recorded by a physician and the study physiotherapist. All complications and adverse events were registered intraoperatively and postoperatively, and also after discharge. Any hospital re-admissions during the 3-month follow-up period postoperatively were also recorded. An evaluation of patient satisfaction was done using a 4-grade verbal rating scale (excellent = 4, good = 3, inadequate = 2, poor = 1) during the first 24 postoperative hours and after 7 days. A power analysis was done before the start of the study using morphine consumption over 48 hours postoperatively as the primary endpoint. The Mann-Whitney U test was used for the analysis of the primary endpoint (morphine consumption) since we found that the data were not normally distributed. Mann-Whitney U test was used to assess pain scores and the Bonferroni-Holm method was used to correct for multiple measures. Hospital stay, and patient satisfaction scores were also analyzed using the Mann-Whitney U test. Dichotomous data were analyzed using the chi-squared test or Fisher's exact test, as appropriate. Values of $p < 0.05$ were considered to be statistically significant.	Median morphine consumption during the first 48 h postoperatively was lower in group A than in group P: 18 (1–74) mg vs. 87 (36–160) mg ($p < 0.001$), i.e. there was a median difference of 69 (95% CI: 47–86) mg. The proportion of patients who requested ≥ 5 mg morphine during the first 24 h was significantly less in group A than in group P (0/23 vs. 10/24) ($p < 0.01$). Median total analgesic consumption (tramadol + morphine) during the first 48 postoperative hours was 54 (4–114) mg and 109 (37–221) mg, respectively ($p < 0.001$). Median VAS pain score was statistically significantly lower in group A than in group P at 3, 6, 12, 21, 22, and 27 h. On movement, median VAS pain score was statistically significantly lower in group A than in group P at 3, 6, 12, 22, 27, and 48 h. Median time to home readiness was shorter in group A than in group P, 3 (1–7) vs. 5 (2–8) days ($p = 0.03$). The median length of hospital stay (LOS) was shorter in group A than in group P, 4 (2–8) days vs. 6 (3–10) days, but this was not statistically significant ($p = 0.06$). Patient satisfaction scores differed between the groups on day 1 ($p < 0.001$) and on day 7 ($p = 0.02$). No major adverse effects were reported.	**Checklist:** -Did the trial address a clear question? Yes -Was the assignment of patients to treatments randomised? Yes -Were all patients who entered the trial properly accounted for at its conclusion? Yes -Were patients, health workers and study personnel 'blind' to treatment? Yes -Were the groups similar at the start of the trial? Yes -Aside from the experimental intervention, were the groups treated equally? Yes -How large was the treatment effect? Large, see results. -How precise are the estimates of the treatment effect? Precise, see results. -Can the results be applied to the local population? Yes -Were all clinically important outcomes considered? Yes -Are the benefits worth the harms and costs? Yes **Limitations** No intraoperative placebo. Surgeons and surgeon nurses were not blinded but did not take part postoperatively or in the study.