Study Protocol

A randomised controlled trial:

Delivery of local anaesthesia through adductor canal catheter after total knee arthroplasty

(DETACH-TKA)

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Protocol Synopsis

Study Title:	A randomised controlled trial: Delivery of local anaesthesia through Adductor Canal catheter after Total Knee Arthroplasty (DETACH-TKA)
Objective(s):	• To find a superior technique (between two methods) of delivering local anaesthesia through an adductor canal catheter after total knee arthroplasty (TKA). • To improve perioperative care pathways for patients having TKA, locally and beyond.
Study Design:	• Prospective, randomised controlled trial comparing continuous infusion of local anaesthesia (5mls/hr of 0.2% Ropivacaine) with programmed intermittent bolus (10mls of 0.2% Ropivacaine bolus every 2 hours) down an adductor canal catheter after TKA. • The local anaesthesia will be administered for 48 hours after commencement in the postoperative care unit (PACU). • Aside from the difference in local anaesthesia delivery down the adductor canal catheter, both groups will receive the same care. Primary outcomes will be total opioid consumption over 48 hours (conversion to total oral morphine equivalents). Secondary outcomes will include Quality of Recovery (QoR-15) questionnaire, time to first assisted mobilisation, number of doses of antiemetic, hospital length of stay, timed up-and-go tests, and side effects at specified time intervals (24, 48, 72 hours after commencement of study infusion).
Subject population and duration:	Patients undergoing a primary total knee arthroplasty at Counties-Manukau District Health Board facilities. We expect the study to be completed in 6-9 months.

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1. Project Overview

1.1 Principle Purpose

Patients may experience significant pain following Total Knee Arthroplasty (TKA) which can delay rehabilitation and result in poorer short and long term outcomes. The use of an adductor canal catheter for two to three days after surgery can significantly reduce opiate analgesic consumption, improve patient satisfaction, and increase the ability to participate in rehabilitation.

The primary aim of this project is to compare and determine the superior technique for the delivery of local anaesthesia down the adductor canal catheter following TKA. This study is designed so that participants are randomized into two groups in a 1:1 fashion; one group will receive a continuous infusion of local anaesthetic (5mls/hr of 0.2% Ropivacaine), and the second group will receive a programmed intermittent bolus (PIB) of 10mls of 0.2% Ropivacaine every two hours. This is a positive-control study with no placebo group. The local anaesthetic will be delivered for 48 hours after commencement in the postoperative care unit.

There is evidence that the use of PIB leads to improved postoperative analgesia as seen by reductions in opiate consumption without side effects. Asides from the difference in local anaesthesia delivery down the adductor canal catheter, both groups will receive the same care as outlined in research methodology.

This study may identify the superior method of administration of local anaesthetic so that future patients undergoing a TKA can have a better experience, and speedier recovery.

1.2 Background

Total knee arthroplasty (TKA) is offered to patients with significant disorders of the knee arising from ageing, degenerative disease or after trauma. With the ageing population, this procedure will become more frequent and consume increasing amounts of health care resources (1). Current guidelines for TKA patients place an emphasis on early mobilisation and discharge to back to the community for home-based rehabilitation (2).

Despite the potential for considerable functional improvement after surgery, TKA is a painful procedure (4). The perioperative analgesic management is one area in which the anaesthetist can influence patient satisfaction and early joint function. To facilitate early mobilisation and rapid discharge, there has been a shift away from traditional techniques that produce systemic side effects or motor weakness - both which hamper post-operative rehabilitation efforts (2,5).

At Counties Manukau Health, the use of high-volume infiltration of low concentration local anaesthesia (LIA) has become the cornerstone of pain management following TKA. This technique is supplemented with multimodal oral analgesia and/or peripheral nerve catheters. A recent study conducted at Counties Manukau confirmed the relative safety of LIA with no observations of toxicity after recording peak local anaesthesia levels between six and twenty-four hours after surgery indicating that there is capacity for additional local anaesthetic use in the perioperative period (6).

As the levels of local anaesthetic begin to fall, evidence from randomized controlled trials and metaanalyses suggest analgesic efficacy of LIA begins to wane (7). To prolong the duration of effective non-opioid analgesia, the anaesthetist can place a

peripheral nerve catheter under ultrasound guidance near the nerves supplying sensation to the operative knee. One such example is the adductor canal catheter (ACC) which provides ongoing pain relief by using local anaesthesia to dampen pain signals generated from the operative site (8,9). The ACC prolongs analgesia without significant motor blockade; patients are less reliant on opioid analgesia and are able to participate in rehabilitation. Evidence from randomised controlled trials suggests that the ACC is a safe intervention which is complementary, and may enhance, the effect of LIA (10).

Post-operative use of an ACC after TKA was first trialled at Counties-Manukau Health in 2015 and it has increasingly been utilised by anaesthetists to achieve the goals as outlined above. In 2018, the Department of Anaesthesia and Pain Medicine enrolled patients in an international trial to determine the most effective site of catheter insertion, the results of which are yet to be published.

There is considerable debate as to what constitutes the most effect method of local anaesthetic administration through peripheral nerve catheters (11). Two potential options include the continuous administration of a fixed amount of local anaesthetic each hour or the use of a programmed intermittent bolus (PIB) whereby a bolus of local anaesthetic is provided every one to two hours through the catheter. PIB may result in greater spread of local anaesthetic which may lead to improved analgesic outcomes (12). Our department has recently completed a meta-analysis which concluded that PIB may be more efficacious, especially for lower limb catheters, than continuous local anaesthetic administration. The benefits seen included a reduction in total local anaesthetic and opioid consumption with no deleterious effect on patient satisfaction or side effects (article submitted for publication).

1.3 Patient Population

This is a study of two techniques of local anaesthesia delivery down an adductor canal catheter in patients who will have an elective unilateral primary total knee arthroplasty through Middlemore hospital and Manukau Super Clinic.

The cohort of patients undergoing this procedure tend to be older, with the majority between 50 to 80 years of age with no discrimination by either sex or ethnicity. Currently, Counties-Manukau Health performs approximately 450 TKAs per annum at Middlemore Hospital and Manukau Surgical Centre.

With the ageing population, we project that the number of patients undergoing TKA will continue to grow in the years to come. Optimisation of our local care pathways is vital to ensure patients receive cost-effect evidence-based best practice. With this study, we aim to improve on our care pathways to aide future patients undergoing a TKA in our institution and beyond.

1.4 Number of Patients

The study size will depend on the power calculation. This information is yet to be collected. Similar trials testing for differences in effect between continuous and intermittent bolus techniques have enrolled between 40 to 60 patients. Once the clinically significant treatment effect has been determined, we will calculate the sample size using standard techniques with $\alpha = 0.05$ and $\beta = 0.2$

2. Research Methods

2.1 Study Design

This is a prospective randomized controlled trial for patients undergoing an elective, unilateral primary total knee arthroplasty. We aim to randomly allocate participants to one of two groups in a 1:1 fashion. The first group will receive a continuous infusion of local anaesthetic whereas the second group will receive a programmed intermittent bolus. Asides from this difference, the participants will all receive routine care after their TKA; this is a positive-control study in which there will be no placebo group. Both the participants and the research nurse assessing patient outcomes will not be aware of group allocations.

2.2 Inclusion Criteria

We aim to enrol patients undergoing primary TKA in our institution prior to the day of surgery in the preadmission clinic or on the day of surgery at the time of surgical and anaesthetic consent. Adequate time for patient questions and a plain language explanation sheet will be provided to aid patient consent. The study will be completed at Middlemore Hospital and Manukau Surgical Centre. Consultation with the Maori and Pacific representatives will be sought as per current HDEC standards.

2.2 Exclusion criteria

- Refusal or inability to consent.
- Analgesic technique involving epidural or peripheral nerve blockade (single shot or continuous techniques)
- Nerve catheter placed outside accepted range (distal to femoral triangle down to the adductor canal)
- Allergies to medication used in the study or its constituents
- Significant kidney and liver dysfunction (CrCl < 30mls/min, AST/ALT >2x upper limit of normal)

- Surgical procedure performed outside of Counties Manukau Health facilities.
- Failure to site adductor canal catheter in the appropriate location.
- Patients on >30mg/day of oral morphine equivalent for any reason.
- Patients outside the specified age range of 18-80 years.
- Patients at extremes of weight e.g.<50kg or >150kg
- If surgical team do not wish to take part or give individually tailored treatment that violate study protocol.

The Anaesthetic and Surgical management of patients enrolled in this study is largely at the discretion of the treating specialists after discussion with the patient. An anaesthetic pro forma is suggested below – data surrounding deviation from this pro forma will be collected and included in the final analysis.

2.3 Suggested Perioperative Pro Forma

1. **Starvation / Nil by mouth status**: as per current anaesthetic department guidelines; 6 hours for solid food, 4 hours for free oral fluids, and 2 hours for clear oral fluids.
2. **Premedication**: Paracetamol 1 gram or 20mg/kg in patients less than 50kg.
3. **Primary anaesthetic technique**: spinal anaesthesia with either isobaric or heavy bupivacaine 0.5% to a maximum of 3ml (15mg). No additives (e.g. intrathecal morphine or fentanyl) are permitted.
4. **Sedation**: Midazolam 1-2mg may be used to help facilitate spinal anaesthetic placement. During surgery, Propofol either by constant infusion or target controlled infusion (TCI) may be used for patient satisfaction and safety.
5. **General Anaesthesia**: While it is suggested that general anaesthesia is avoided, this may be required in the event of the crisis or at the request of the patient and/or

the anaesthetist. If general anaesthesia is to be used, we suggest Propofol TCI as the primary agent.

6. **Rescue analgesia**: fentanyl boluses of 25-50mcg every 5 minutes can be used in conjunction with the sedation technique described above in the event of patient discomfort. This should be recorded on the patient chart and the reason for the administration noted on the study case reporting form (CRF).
7. **Local Infiltrative analgesia (LIA)**: Ropivacaine 0.2% (2mg/ml) 150mls (total 300mg) with adrenaline 5mcg/ml (total 750mcg) should be injected prior to implantation of the prostheses. The technique of injection should be methodical and follow the current standard of practice at Counties Manukau Health.
8. **Supplementary agents**: in patients where nonsteroidal anti-inflammatory drug (NSAID) use is not contraindicated, parecoxib 40mg should be given intraoperatively. This should be followed by celecoxib 100mg BD for the duration of hospitalization.
9. **Antiemetic Therapy**: Dexamethasone (4-8mg) and Ondansetron (4mg) should be administered as antiemetic therapy if not contraindicated.
10. **Intravenous fluid therapy**: at the discretion of the treating anaesthetist. In routine patients without haemorrhage, 1000-2000ml of balanced crystalloid solution is suggested.

In addition to these guidelines, the use of indwelling bladder catheter and tranexamic acid use is at the discretion of the treating surgeon and anaesthetist. Patient mobilisation should take place on the day of surgery and will be assisted by the ward based nursing and allied health staff.

2.4 Placement of the Adductor Canal Catheter

At the end of surgery after sterile surgical dressing have been applied, an ultrasound guided adductor canal catheter will be placed on the operative limb using an aseptic technique. A multiorifice catheter (e.g. Contiplex or Contiplex C *B.Braun AG, Melsungun, Germany)* should be placed either within the distal femoral triangle or within the adductor canal deep to the Sartorius muscle. At least 2cm catheter should be left beyond the end of the needle. The catheter can be secured with both tissue glue and/or a catheter anchoring device prior to the administration of a sterile dressing.

No local anaesthetic will be administered down the catheter until the attachment of the prescribed infusion in the post-anaesthesia care unit (PACU). Randomisation will have taken place using opaque envelopes. Both the participants and the research nurses will not be aware which treatment a particular patient is receiving whereas the PACU nurses involved in the programming of the infusion pump and attaching the infusion to the patient will not be blinded. Participants will be randomised to receive either:

1. Continuous infusion group – 5 mls/hr of ropivacaine 0.2% for 48 hours
2. Programmed intermittent bolus group – 10mls ropivacaine 0.2% every two hours for 48 hours.

The time of infusion commencement will be noted down and the trial will run for 48 hours from this point. During this trial period, the assessments will take place at specified time points; 24 hours, 48 hours and 72 hours after the commencement of the infusion.

2.5 Trial Assessments

Primary outcome:

Total opioid consumption over 48 hours. This will be converted to oral morphine equivalents as per the methods prescribed by the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists.

(*http://fpm.anzca.edu.au/documents/opioid-dose-equivalence.pdf*)

Secondary outcomes:

- Quality of Recovery (QoR-15) scores collected 24 and 48 hours after commencement of the study infusion.
- Time to first assisted mobilisation measured in minutes after discharge from PACU.
- Passive range-of-movement on day 1 and day 2, 24 and 48 hours after commencing the study infusion.
- Number of doses of antiemetic required over the 48-hour study period.
- Hospital length of stay measured in days.
- Side effects including nausea and vomiting, pruritis and sedation (Pasero opioid-induced sedation scale) collected daily.
- "Timed up and go" or TUG test 24, 48 and 72 hours after commencement of study infusion; TUG test is the time in seconds it takes the patient to stand from the chair, walk 3 meters, turn around and sit down again.
- Passive range-of-motion; the range of knee flexion will be recorded by the research nurse using a goniometer at the same follow up time intervals.

Post-operative Analgesia:

- Regular paracetamol (1gram Q6h) and celecoxib (100mg BD) unless contraindications exist.
- Do not prescribe sustained release opioid preparations (OxyContin or M-Eslon)
- Avoid prescribing IV Morphine and Patient Controlled IV Analgesia, unless strong reasons exist (e.g. Chronic pain states or pre-existing therapy).
- Patient will have access to the following PRN analgesia if required.

- Sevredol: Morphine immediate release 10-20mg PO Q2 hours PRN
- Tramadol 50-100mg either PO or IV Q6 hours PRN
- Oxycodone Immediate release (OxyNorm): 5-10mg PO Q2 hours PRN

A trial safety and data adjudication committee with three members independent from the study will be established to adjudicate serious adverse events and determine the need to stop the administration of trial drugs. Given the established safety of the medicine and technique, it is anticipated that this should be infrequent.

2.6 Benefits to Participants

Potential benefits to participants include helping healthcare providers determine the most efficacious mode of local anaesthetic administration through an ACC. This may lead to changes in care pathways at Counties-Manukau Health and could have considerable benefits for future patients undergoing TKA. Depending on the individual's mindset, the participation in clinical research can lead to considerable satisfaction. As there is no control or placebo group, active therapeutic interventions will not be withheld, participants are not at risk of missing out on the therapeutic benefit of an ACC.

For both the District Health Board and the wider anaesthetic community, the results of this study could provide some clarification to changes which may be required in our pathways for patient care after TKA. Should benefits be seen in mobilisation, satisfaction or hospital length of stay, there are obvious economic effects including the reduction in overall healthcare costs and improved compliance with rehabilitation protocols.

3. Statistical Considerations

The statistical assessment of trial data will be devised and performed by a biostatistician. Patient demographic, surgical and anaesthetic factors will be recorded and tabulated. Demographic data will be presented as number (percentage) for discrete observation and mean (standard deviation) for continuous parameters.

For primary outcome (analgesic consumption in oral morphine equivalents) a test for differences in means / variances will be performed as guided by the data. Statistical test will be two-tailed with $p=0.05$ used as the threshold for statistical significance. Where possible, the clinical relevance of a statistical test will be provided in addition to the p-value. Similar testing strategies will be used for the secondary outcomes with differences in discrete observations (e.g. yes/no data) determined using the Fisher Exact test.

4. Data collection and retention

Data collection will be performed primarily by a research nurse specialist and/or investigator who will visit postoperatively to obtain the necessary parameters on paper form – this will be stored inside a secure cabinet in the department of anaesthesia and pain medicine. A Microsoft Excel spread sheet will be designed with various worksheets for data collection and analysis – this will be password protected and only accessed by approved investigators from within the Counties Manukau Health network.

Only those involved in the study will have access to study data. The study data will be kept for a minimum of 10 years as required by the Retention of Health Information's

regulations 1996. We have no plans beyond this study to use any information obtained – should this change; additional consent will be sought.

5. Ethics and Responsibility

This study will be conducted in strict compliance to protocol and with the approval of the local research review committee. The investigators, David Choi and Nicholas Lightfoot, can declare that they do not have any financial or other interests in the study.

6. Conclusion

This study aims to identify the superior technique of local anaesthetic delivery down an adductor canal catheter after a primary total knee arthroplasty. This study will allow us to examine and optimise our local care pathways for patients undergoing TKA, as well as inform and influence other healthcare providers further afield.

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