PROTOCOL: Intraosseous Regional Administration of Diclofenac (IRAD) in Primary TKA Study

Version 3

Date: 23 Oct 2021

A prospective, double-blinded, randomised controlled trial of Intraosseous Regional Diclofenac vs Intravenous Diclofenac for Postoperative Pain Management in Primary Total Knee Arthroplasty

---

Contact/Lead Investigator:

Simon Young

Consultant Orthopaedic Surgeon

Southern Cross North Harbour

Glenfield

Auckland

New Zealand

Intraosseous Regional Administration of Diclofenac (IRAD) in Primary TKA Study: A Prospective, Double-Blinded, Randomised Controlled Trial Comparing the Analgesic Efficacy of Intraosseous Regional Diclofenac and Intravenous Diclofenac for Postoperative Pain Management in Total Knee Arthroplasty

Background

Primary total knee arthroplasty (TKA) is a commonly performed procedure for arthritis of the knee, to improve mobility and quality of life by reducing pain. However, patients will often experience moderate to severe postoperative pain which can in turn impair patient rehabilitation, thus impacting on their overall outcome and satisfaction for the operation [1], with pain being a cited reason for patients to delay having surgery [2].

Systemic opioids have been the mainstay of perioperative pain management, however opioids come with important side effects [2]. Potential adverse effects of opioids detrimental to patient recovery include sedation, respiratory depression, confusion, constipation, nausea, vomiting, pruritus, and urinary retention. These adverse effects have been associated with increased length of stay and poorer overall outcomes [2,3]. Thus, multimodal analgesia is used as a strategy to reduce systemic opioid consumption by utilising other methods of pain relief, while maintaining adequate analgesic effects.

The basis of this study is to investigate the efficacy of intraosseous (IO) regional administration of Diclofenac (Voltaren™), a non-steroidal anti-inflammatory (NSAID), in postoperative pain prevention following primary TKA as part of multimodal analgesia.

Intraosseous Regional Administration (IORA)

The principles of IORA are similar to those of intravenous regional local anaesthetic (IVRA).This technique involves perfusing a limb by injecting local anaesthetic into a vein after tourniquet inflation [9]. The tourniquet acts to cease blood flow in the region of interest, allowing the local anaesthetic to distribute throughout the operative site distal to the tourniquet, thus retaining anaesthesia in the desired area. Various studies have investigated the efficacy of NSAIDs as an adjunct in IVRA, and these have shown benefits for improving postoperative pain relief [14-17].

Likewise, in IORA medication is administered via IO access distal to the tourniquet creating the same effect with additional benefits. In the lower limb, the advantage of IORA is that it avoids the need to

cannulate a foot vein which can be difficult and time consuming and may compromise the sterile field when operating on a knee.

Typically, the IO route is required for critically ill patients needing rapid and reliable resuscitative access if intravascular access cannot be established. This allows for administration of medication, fluids, or blood products. In theory, IO infusions should achieve similar drug concentrations and onset of action to intravenous (IV) access [4]. The IO route provides non-collapsible access to the systemic venous circulation via the bone medullary cavity. Due to the direct access to the central venous system, onset times of medications administered via IO route are similar to IV administration, with some medications even having a prolonged duration of action suggesting that IO access may have a depot effect [5].

There are multiple approved sites of insertion for IO needles including the sternum, humeral head, distal radius and ulna, ilium, femur, proximal and distal tibia, depending on the type of IO needle [4]. For this study, the anteromedial aspect of the proximal tibia, 2 cm inferior to the medial joint line, at the level of the tibial tuberosity, is the chosen site of injection. This area provides a flat surface with a thin layer of skin and soft tissue, and in addition with the cortex being thinner in this region, making it the optimal injection site [4, 5]. Furthermore, insertion into the metaphyseal bone of the proximal tibia have been found to allow for faster flow rates [6].

The intraosseous route is equivalent to intravenous, and the application of IORA of various medications has been investigated. IORA of antibiotics for prosthetic joint infection prophylaxis in TKA have shown to yield higher local concentrations of antibiotics, compared to systemic intravenous administration [9], and even with reduced doses higher concentrations were obtained [10, 11]. The theory and expected outcome behind these findings were to provide equal or improved efficacy for antibiotic prophylaxis with reduced systemic side effects [6]. Waisman et al completed a study investigating the use of IORA of local anaesthesia as an alternative to IVRA, using lidocaine (0.25-0.5%) as the medication of choice. In total, 109 orthopaedic operations (both upper and lower limb) were completed under IORA with all but three patients achieving adequate anaesthesia [7].

<u>Why Diclofenac?</u>

Overall, Diclofenac is a relatively well tolerated and safe drug that has been widely used since it has been approved. Its adverse effects are well understood, and if used as directed with the correct precautions, significant adverse events should be avoided.

We are aware that Ketorolac is currently being used overseas for IORA purposes, however it is not readily available for use in New Zealand. Diclofenac solution for intravenous infusion, which is readily available, is indicated in prevention of postoperative pain as well as postoperative pain relief. The study authors currently routinely use IORA of Diclofenac (Voltaren™) in total knee arthroplasty, with anecdotal benefits in postoperative pain relief.

Despite not having easy access to Ketorolac, Diclofenac has been shown to be more efficacious regarding pain relief. A randomised control trial found the mean sum of pain intensity differences (SPID) was significantly better in postoperative orthopaedic patients receiving IV Diclofenac compared with IV Ketorolac [27]. IV Diclofenac was also shown to be superior to IV Ketorolac in dental surgery [28].

Rationale for IORA of Analgesics

IORA of analgesic medication may provide various advantages over other methods of administration or other forms of analgesia for postoperative pain prevention and overall outcomes for patients. This includes:

1) The ability to deliver analgesic medication directly to the surgical area of interest and avoid systemic delivery, thus minimising systemic adverse effects.
2) Achieving higher local concentrations of medication with tourniquet inflation leading to a “pooling effect”, therefore maximising local analgesia and resulting in overall more efficacious pain relief.
3) Potentially prolonged duration of action of the medication given IO access may produce a depot effect.
4) The ability to provide rapid regional administration of medication through an intraosseous cannulation, avoiding the need to cannulate a foot vein.
5) Indirect benefit of lowering postoperative systemic opiate consumption due to more effective pain relief, therefore avoiding or reducing the undesired side effects that come with opioids.
6) With enhanced early postoperative pain control this may allow for a faster recovery through early mobilisation

Patient Evaluation Schedule

Evaluation	History/Pre-op	Post-op first 24 hours (1-5 hrs, 12 hrs, 24 hrs)	Post-op day 1	Discharge date	1 week post-op	Week 2	Week 6
Demographics	**X**						
Medical History	**X**						
Allocated Analgesia	**X**						
PCS	**X**						
PDI	**X**						
KOOS Jr Score	**X**					**X**	**X**
OKS	**X**					**X**	**X**
VAS-P	**X**	**X**			**X**		
MME	**X**	**X**			**X**		
LoS				**X**			
Gait					**X**		
Sleep					**X**		
QoR-15			**X**				
Satisfaction						**X**	**X**

Visit Windows

Definition – Since it is not always possible for subjects to come in for a study visit on the exact date, most protocols allow a certain time period before or after the calendar date; this is known as the visit window. If a subject is not seen during the visit window, that visit will be regarded as a missed visit. Visit windows are calculated in reference to the baseline date, which is the surgery date (intra-op) for this study.

Visit windows:

- Pre-op: within 6 months before date of surgery
- Week 2: +/- 1 week
- Week 6: +/- 2 weeks

Objectives

The primary objective of this study is:

- To demonstrate that preoperative IORA Diclofenac (Voltaren™) is superior to systemic (intravenous) Diclofenac, in providing early pain control following primary total knee arthroplasty (TKA) for osteoarthritis. Visual analogue scale pain (VAS-P) scores will be the primary outcome to compare pain at rest and with standard evoked movement; means will be calculated over 1 week.

The secondary objectives of this study are:

- Comparing MME measurements between the IORA Diclofenac, and systemic Diclofenac groups to demonstrate reduced postoperative systemic opioid use for additional pain relief with IORA technique.
- Quality of life/functional outcome comparisons using the KOOS Jr score, Oxford Knee Score (OKS), numerical rating scales (NRS) of gait/walking ability and sleep.
- Post-operative recovery comparisons using the Quality of Recovery 15 (QoR-15) survey and comparing average length of stay (LoS) for each study group

Questions to be answered:

1. Is IORA of Diclofenac or systemic Diclofenac more effective in managing post-operative pain (as judged by VAS-P scores).
2. Will IORA of combined Diclofenac or systemic Diclofenac result in a more significant reduction in additional systemic opioid use for post-operative analgesia (as judged by MME).
3. Will IORA of Diclofenac or systemic Diclofenac provide better clinical improvement in knee health recovery and outcomes (as judged by KOOS Jr, OKS, NRS gait/walking ability and sleep, QoR-15, LoS).

Study Design

A prospective, double blinded RCT, with a single site cohort.

Patients and Methods

Patients who will be undergoing primary TKA for osteoarthritis will be eligible for this prospective study and randomised into two groups with 23 participants in each, one group receiving IORA Diclofenac (intervention group), and one group receiving IV Diclofenac (control group).

Power Calculation

There is a paucity of data evaluating the efficacy of IORA in pain management following TKA because it is a novel technique, although postoperative pain management is a thoroughly investigated area. Sample size was calculated based on previously published data investigating the efficacy of perioperative Celecoxib (a NSAID) on postoperative pain (VAS pain) after TKA [32]. This study showed statistically significant improvements in VAS pain scores for the intervention group (Celecoxib and PCA Morphine) at 48 hours and 72 hours after TKA, compared to the control group (PCA Morphine only). Mean VAS pain scores (in mm) in the intervention group were 21.3 ± 16.8 at 48 hours, and 17.8 ± 16.6 at 72 hours. Whereas VAS pain scores in the control group were 34.3 ± 15.0 at 48 hours, and 31.7 ± 20.1 at 72 hours.

The minimal clinically important difference is defined as the smallest change in a measurement that signifies an important improvement in a symptom. MCID for VAS-P in acute pain management has a wide range, ranging from 8-40 mm, with a median of 17 mm [29]. In a review across 570 randomised controlled trials on postoperative pain management after total hip and knee arthroplasty, the median MCID for VAS-P was found to be 15 mm at rest and 18 mm during movement [30]. Another study demonstrated the mean MCID for VAS postoperative pain improvement in TKA patients to be 22.6 mm [33]. There is yet to be a standardised value for postoperative VAS-P MCID, but based on recent literature and consensus we have chosen an MCID of 20 mm to suggest clinically relevant improvements in pain relief between the intervention and control groups [34].

Using this data, a priori power analysis was calculated using this data, which found that 22 patients in each arm would provide >95% statistical power to detect the expected difference in pain relief (MCID of 20 mm) at the 5% significance level between IORA Diclofenac and systemic (IV) Diclofenac. An additional patient in each group (5%) will bring each group to 23 patients to account for loss of follow up.

Inclusion Criteria

Informed consent obtained - both written and verbal

Patient undergoing primary total knee arthroplasty for Osteoarthritis

Age ≥ 18 and ≤ 80 years old (inclusive)

Exclusion Criteria

Patient lacking capacity to consent to the research project

BMI ≥ 40

Pregnancy or suspected pregnancy

Pain Catastrophising Scale score ≥ 30 points

Previous infection of knee joint

Rheumatoid/inflammatory arthritis

Undergoing bilateral total knee replacement, revision total knee arthroplasty, or any additional procedure outside of a primary total knee arthroplasty

Precluded from having general anaesthesia

Patients with lower limbs not amenable to effective tourniquet use

Contraindications to Diclofenac:

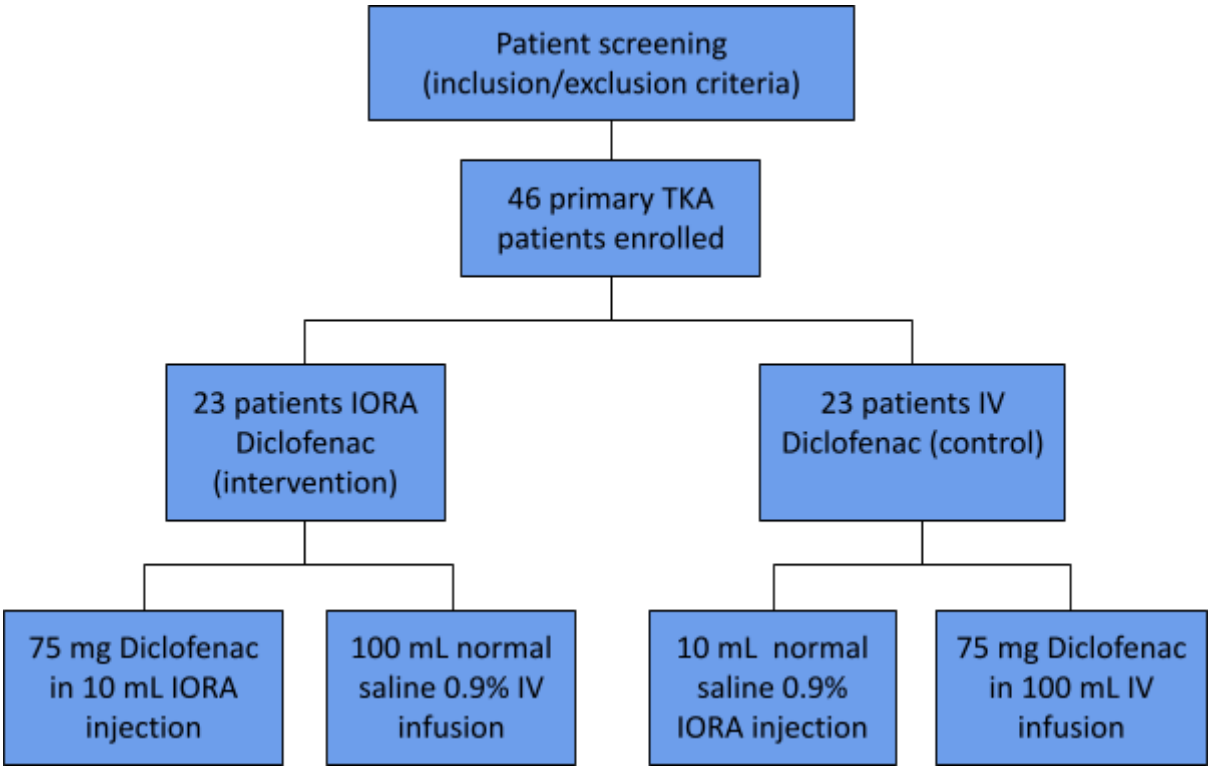
- Established allergy or hypersensitivity to Aspirin or other NSAID - including attacks of asthma, angioedema, urticaria, or acute rhinitis
- Severe renal disease (GFR<30 mL/min/1.73m^2)
- Severe cardiac failure
- Hepatic failure
- Active gastric or intestinal ulcer, bleeding or perforation
- Recent myocardial infarction (within last 12 months)
- History of asthma
- History of haemorrhagic diathesis

Multiple surgeons who regularly perform TKA will carry out this procedure on all patients included in the trial. Prior to all surgeries, each patient will undergo a general anaesthetic (GA) for their procedure, and no patients will have a neuraxial and/or peripheral nerve block. This will involve total IV anaesthesia with IV Propofol and IV fentanyl, as well as Ketamine and/or Clonidine in small amounts as adjuncts to the GA. The airway will be maintained via laryngeal mask airway. As part of usual TKA protocol 2g IV Cephazolin, 2g IV Tranexamic acid, and 16mg IV Dexamethasone will also be administered. The Patient will then be positioned appropriately for surgery and a single cuff tourniquet applied to the upper thigh of the marked limb. Following standard patient preparation

and draping of the appropriate limb, the limb is exsanguinated, and the tourniquet inflated to cease blood flow in the limb at 250-300 mmHg for the duration of the procedure (60-90 minutes). A proximal tibial IO cannula will then be inserted, and the study medication administered into bone immediately before skin incision [6, 7].

There will be two groups into which patients will be randomised; 23 patients will be randomised into each group:

- Group 1: IORA 75mg Diclofenac preoperatively (intervention group).
- Group 2: IV infusion 75 mg Diclofenac preoperatively (control group).



For the patients randomised to the IORA Diclofenac group, following tourniquet inflation a proximal tibial cannula will be inserted. The study medication will be administered via the cannula into bone immediately before skin incision. 75mg Diclofenac (75 mg/3 mL ampoules) will be made up to 10mL with normal saline 0.9% in a syringe to dilute the medication prior to administration. The medication will then be injected as a bolus by the blinded surgeon. Immediately after, 500 mg of Vancomycin in 110 mL normal saline 0.9% will be delivered intraosseously. These patients will also receive a preoperative IV infusion of 100 mL normal saline 0.9% over 2 minutes by the blinded anaesthetist. The infusion will finish at least 3 minutes prior to tourniquet inflation.

The patients randomised into the second group will receive an IV infusion over 2 minutes of 75 mg Diclofenac (75 mg/3 mL ampoule) diluted to 100 mL with normal saline 0.9%, to finish at least 3 minutes prior to tourniquet inflation, by the blinded anaesthetist. Diclofenac (Voltaren™) 75 mg/3 mL solution has been approved by New Zealand Medsafe for intravenous infusion, but requires to be diluted. There are injectable Diclofenac formulations which can be administered as bolus, however these are not available in New Zealand. 10 mL of normal saline 0.9% will be given via IO after tourniquet inflation, followed by the same preparation of Vancomycin by the blinded surgeon.

An unblinded researcher (not the surgeon or anaesthetist) will prepare the medication as described above, according to the participant's group allocation. The preparation for IV infusion will be given to the blinded anaesthetist, and the preparation for IO injection will be given to the blinded surgeon.

All patients will also receive intraoperative local infiltration anaesthesia prior to skin closure in the form of 150 mL of 0.2% Ropivacaine with 0.3mcg of Adrenaline 1:1000 (0.3 mL). This is placed intra-articular and in the tissue surrounding the knee. Weight based dosage of ropivacaine will be used if patients are small.

Patients in all study groups will receive a standardised regimen of pain relief (unless certain medications are contraindicated) post-op as an inpatient and on discharge. Post-op analgesia includes IV Morphine 1-2 mg (in recovery only), Paracetamol 1 g PO QID, Celecoxib (dose will be prescribed according to weight/age), Tramadol modified release 100 mg PO BD, Gabapentin (dose will be prescribed according to weight/age), and Sevredol 10 mg PO Q1H PRN. The same preparation of Paracetamol, Celecoxib, Tramadol, and Gabapentin will be prescribed on discharge, but Sevredol will be reduced to 10 mg PO Q4H.

Informed Consent

An investigator will verbally inform potential study candidates of the purpose of the study, study duration, relevant procedural details, and study evaluations. Benefits that may result from the trial (during the study and for future patients) will be discussed, and also any foreseeable risks. Patients will then be given time to read, understand, and sign the study-specific Participant Consent Form if agreeable to participating in the study. Confidentiality of the participants will be maintained at all times, and de-identified patient information will be used during study analysis.

Participants will be informed that they are free to refuse participation, and medical care will not be compromised if they decline or withdraw from the study.

In order to be enrolled in the study, a signed and dated Participant Consent Form must be obtained first. The original will be kept by the investigator, with a copy being provided to the patient, and another copy placed in the patient's hospital medical record.

Should a patient undergo any study procedure without signing a Participant Information and Consent Form, the Investigator must notify the applicable Ethics Committee of the deviation, detailing the circumstances which resulted in the failure to obtain informed consent. The Investigator will then follow Ethics Committee instructions on how to handle the patient/situation and obtain consent.

Randomisation

Allocation Concealment

This will be achieved via a complete randomisation process using computerised sequence generation (random number generator) in a 1:1 ratio. Sealed, opaque envelopes which have been sequentially numbered will be used as the method of concealment. The envelopes will contain a randomised group allocation and instructions of medication preparation for administration. These will be prepared by an independent member of staff. The envelopes are to be sequentially numbered, as per the generated sequence, in advance for allocation to patients once they have consented to the trial. Once a patient has met the criteria for enrolment and has given informed consent, they will be allocated a randomisation envelope by the investigator or designee. Envelopes will be opened sequentially only after the participant's name has been written on the appropriate envelope. The investigator or designee will note the randomisation number in the patient's Case Report Form and this will be used as the patient's study ID number. Patient's will be blinded to their group allocation.

A patient information leaflet will be provided to the patient at their preoperative clinic appointment. Randomisation is to occur at the time of consent (which is usually the day prior to surgery) to allow for the appropriate orders to be made to ensure the study medication can be administered on time. The assigned envelope will be handed to a researcher on the day of the procedure, who will begin preparing the study medication for the appropriate study group.

Blinding

Patients, surgeons, and anaesthetists will be blinded to group allocation. Patients will be under general anaesthetic at the time of study medication administration, so will not be aware of which mode of study medication has been given. An unblinded researcher will prepare a 10 ml syringe with either normal saline 0.9% (control group), or 75mg Diclofenac made up to 10 mL with normal saline 0.9% (intervention group). The fluid will be passed onto the sterile field for administration by the treating surgeon.

An infusion of either 75mg Diclofenac made up to 100 mL with normal saline 0.9% (intervention group), or 100 mL normal saline 0.9% (control group) will be prepared by an unblinded researcher and handed over to the anaesthetist (blinded) for the preoperativeIV infusion.

Evaluations/Patient Outcome Measurements

Patient Demographics

A record of the patient's date of birth, age, gender, weight, height, BMI, and medical history will be obtained pre-operatively at time of consent.

Patient Catastrophising Scale (PCS)

A self-reported measure which assesses catastrophic thinking in the context of actual or anticipated pain. Pain catastrophising is associated with poor pain treatment response in patients with chronic pain [35].

Pain Disability Index (PDI)

A widely used tool for determining pain-related disability. It measures the degree to which chronic pain disrupts different aspects of life.

KOOS, Jr Survey

The Knee Injury and Osteoarthritis Outcomes Score for Joint Replacement survey provides a single score that represents "knee health" as it combines pain, symptoms, and functional limitations [31]. It is a patient reported outcome measurement instrument developed to assess the patient's opinion about their knee and associated problems.

Oxford Knee Score (OKS)

A patient-completed 12-item questionnaire, designed specifically for patients undergoing total knee replacement. Relates to an individual's level of function, activities of daily living, and how they have been affected by pain. Each of the 12 items has 5 scoring categories. It is short, practical, reliable, valid and sensitive to clinically important changes over time.

Visual Analogue Scale Pain (VAS-P)

A graphic VAS will be used as a measurement instrument for patients to indicate their level of pain on a scale from 'No Pain' to 'Worst Pain Possible'. VAS is a continuous spectrum to represent pain.

Morphine Milligram Equivalent (MME)

MME is the amount of morphine in milligrams equivalent to the strength of the opioid dose prescribed. This measurement will allow for a standardised comparison of opioid use between study groups.

Patient Satisfaction

Numerical rating scale (NRS; 0-10) for grading a patient's satisfaction with their knee replacement, from 'completely dissatisfied' to 'completely satisfied'.

Gait/Walking Ability and Sleep

NRS (0-10) for grading how pain has interfered with a patient's walking ability and sleep over the past 24 hours, from 'does not interfere' to 'completely interferes'.

Average Length of Stay (LoS)

Each patient's length of stay in hospital will be recorded from day of admission to day of discharge.

Quality of Recovery (QoR-15)

A patient reported outcome questionnaire to measure the quality of recovery after anaesthesia, which is important in determining early postoperative health status of patients.

Outcomes

Preoperative Outcome Measurements

The following outcome measurements will need to be completed by patients prior to their surgery. Baseline scores will be averaged for each study group:

- PCS - A PCS score of ≥ 30 represents clinically relevant catastrophising and will exclude patients from the study.
- PDI
- KOOS, Jr
- OKS
- Preoperative VAS-P score
- Preoperative opioid use (MME) - Participants will be required to report any and all opioid pain medications (including Tramadol and Codeine) they use as well as the average daily amount of opioid medications in milligrams that they take. For example, 20 mg of Sevredol daily. This will be converted into a preoperative baseline MME.

Postoperative Outcome Measurements

The primary outcome of this study will be patient pain levels during the early stages of recovery following primary total knee arthroplasty. To monitor this, pain at rest scores will be recorded by the patient using the Visual Analogue Scale (VAS; 0-100 mm from “no pain” to “worst pain possible”). The distance between “no pain” and the patient-made mark is to be measured to the nearest 1 mm.

Post-operatively, once the patient has arrived at the recovery unit, pain scores are to be recorded at the following time points: 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 12 hours, and 24 hours post-op. These numbers will be recorded by a recovery nurse who will be blinded to the treatment group, and by a treating physio the following day. Patients will also record twice daily VAS-P scores at 8am and 5pm from post-op day 1, up to post-op day 7, into a pain diary supplied to them. These twice daily recordings will be used to calculate daily averages of pain scores. All VAS-P scores are to be recorded for ‘pain at rest’.

The minimal clinically important difference (MCID) of 20 mm for VAS-P scores will be used to determine the clinical significance of pain relief in the intervention group compared to the control group.

Secondary outcomes which focus on function, pain, satisfaction, and health related quality of life:

- Total Morphine Milligram Equivalent (MME) of additional postoperative opioid medications required for 1 week post-op (from post-op day 0 to post-op day 7).
- Quality of recovery after anaesthesia (as per QoR-15 survey), recorded post-op day 1.
- NRS for gait/walking ability, sleep. To be recorded for 1 week post-op.
- Participant length of hospital stay, from date of admission to date of discharge.
- NRS for patient satisfaction, recorded at post-op weeks 2 and 6.
- KOOS, JR scores at post-op weeks 2 and 6.
- OKS at post-op week 6.

Indirect measure of pain will be gauged from the total MME dosing for each patient which will be an indicator of postoperative opioid use burden. Patients will be required to record in their pain diaries the amount, in milligrams, of additional opioid medication they are taking per day up to post-op day 7, which will then be converted into daily MME. Patients will also be required to record on a NRS how much pain has interfered with their walking ability and sleep over the previous 24 hours, up to post-op day 7 in their pain diaries.

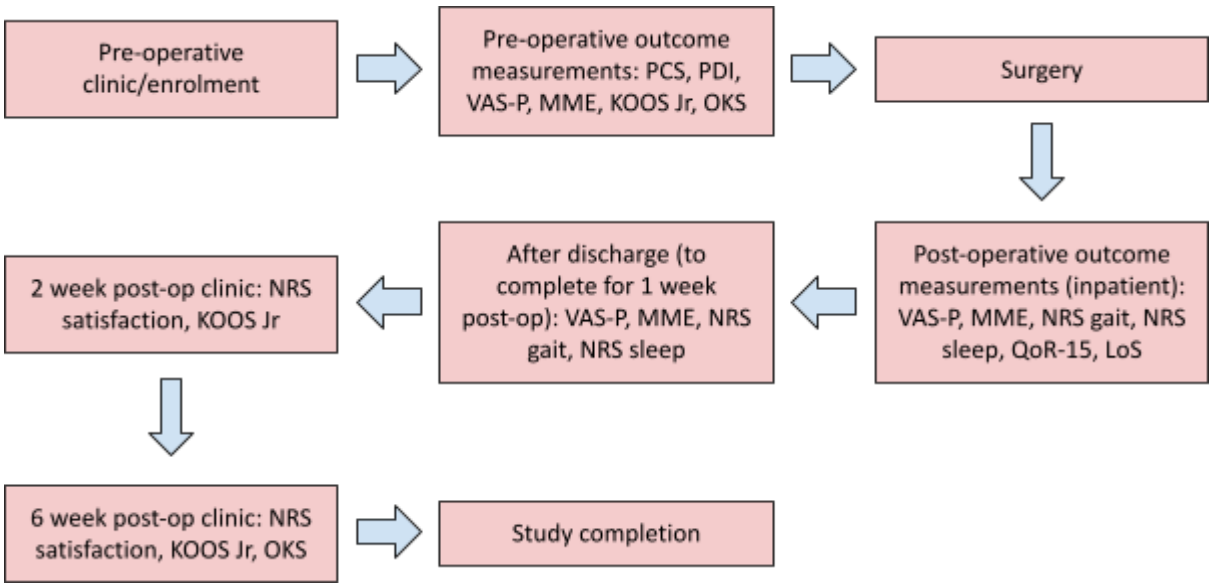
An automated texting service will be used to remind patients to fill out their pain diary.

Length of stay from date of admission to date of discharge will be recorded for all participants on their pain diaries. Average length of stay will be calculated for each study group and compared.

Participants will be followed up in a 2 week post-op clinic where the pain diaries are to be collected. At this clinic, participants will be required to complete a KOOS Jr survey and NRS for patient satisfaction relating to their knee replacement. At the 6-week post-op mark patients will be seen in clinic again and will be required to complete a KOOS Jr survey, patient satisfaction NRS, and OKS. The means of these outcomes will be compared between the study groups at each particular time point.

Participants will be provided patient information leaflets detailing potential adverse effects of Diclofenac. If any adverse effects occur, participants are to report to nursing staff, who will inform the treating doctor/researcher. We predict side effects from a single preoperative dose of Diclofenac are unlikely to arise after discharge i.e., a few days post-op.

Study Timeline



Data Capture and Analysis

Data will be recorded on Case Report Forms (CRFs; includes patient pain diaries). An investigator will complete and sign forms once they are completed by patients. The data will then be entered onto a secure excel spreadsheet by a research assistant. The original paper CRFs are to be stored securely, and archiving to be undertaken in accordance with ICH/GCP guidelines.

Means, standard deviation, and 95% confidence intervals will be calculated for the participant VAS-P scores at each recorded time interval as the primary objective of the study. A general linear model or generalised linear mixed model, followed by independent two-sample t-test or Wilcoxon non-parametric rank sum test will be used to analyse the data. VAS-P scores will be pooled according to the appropriate study group for comparison between the study arms. An MCID of 20 mm will be used to determine a clinically significant difference in pain management (but not necessarily statistical significance).

For secondary objectives, independent two-sample t-test or Wilcoxon non-parametric rank sum test will be used to compare means of MME, LoS, QoR-15, satisfaction, gait, sleep, OKS, KOOS Jr scores between the intervention group and control group.

The intended statistical test used will be dependent on the distribution of the data collected. This will be determined by appropriate normality and homogeneity testing of the data. If requirements

are not met, a transformation may be applied, which will likely be logarithmic. Adjustments will be made accordingly based on the data obtained.

Baseline characteristics and preoperative survey scores will be compared using a two sample t-test or Wilcoxon non-parametric rank sum test. Gender comparisons between the two study groups will need to be analysed using a two-way analysis of variance (ANOVA) or in the case of non-parametric testing, Kruskal-Wallis test.

Adverse events will be recorded separately and reviewed by investigators for relevance to the procedure/intervention as well as commonalities. Frequency and percent distributions will be presented in tabular form and logistic regression will be used for comparison of the study groups.

The statistical principles of this protocol have been reviewed by a Consultant Statistician who will also oversee statistical analysis.

Selection Criteria for Investigators/Sites

- The investigator(s) participating in this study is(are) qualified Orthopaedic surgeon(s).
- Research assistants and study staff will be under the direction of the Principal investigator.
- Conflicts of interest (including financial assistance from other parties) will be declared by Investigators and research personnel before starting the trial.
- A list entailing any persons, their qualifications, and their roles relating to the trial, must be kept by the investigators.
- Sites must have adequate facilities and trial staff, as well as demonstrate that adequate participant recruitment is likely possible.
- Investigators must provide the appropriate medical care for participants if an adverse event were to occur during or following the trial (that is deemed related to the trial).
- A favourable Ethics Committee endorsement of the trial protocol, as well as any information provided to participants, must be obtained prior to investigators commencing the trial.
- The investigator/institution shall permit trial related monitoring, audits, ethics review, and regulatory inspections. Trial related data/documents will be made accessible under these circumstances.
- The trial must be conducted according to the approved protocol. Any deviation from the protocol must be documented for later review.
- No deviation from the approved protocol may occur without review and endorsement from the Ethics Committee, unless necessary to prevent imminent harm to participants.

- Investigators must ensure participants have given informed, written consent, with a thorough understanding of all trial procedures and risks.

Admittance of Patient

Prior to enrolling participants or beginning the study, written approval from the Ethics Committee and Governance must be obtained by the investigator.

Each patient must be reviewed pre-operatively in accordance with the inclusion and exclusion criteria by the investigator.

Upon signing the consent form and patient information sheet, a patient will be identified as a participant within this clinical trial.

Patient Accounting

An informed consent log consisting of details (NHI number and initials) of patients, who have completed the consent form, will be kept by the investigator.

Clinical trial data will be regularly monitored throughout the trial. Any trends and adverse events will be noted during the process. Participant voluntary withdrawal or loss to follow-up will be documented on a Study Completion Form.

Data Quality Assurance and Data Safety Committee

Case Report Forms will be reviewed by an investigator or designee to ensure completeness and adequate accuracy, as well as for evidence which may indicate patient risk. Any noted discrepancies will be resolved by the investigator or designee. Attempts will be made to obtain data if possible, where the data is incomplete.

The clinical research team will be responsible for monitoring the trial site to ensure compliance with the study protocol and capture of any data or complications not already documented. Data will also be verified from source documents. A Data Safety Committee has not yet been formed, but will be formed prior to beginning the study. This should comprise of the Principal Investigator, a statistical advisor and a patient advocate will be formed to review the data and any adverse event forms .

Management of Concurrent Events

Concurrent Illness/Procedures

Where participants experience inter-current illnesses or adverse events, any required concurrent procedures or medications will not be restricted during the study. Given the demographics of patients receiving total knee joint replacements, it can reasonably be expected that this may occur.

Withdrawal from Study

All study participants will be advised that they may voluntarily withdraw from the study at any stage, for any reason, and they have no obligation to state their reasoning. This will not affect their medical care. Even so, efforts will be made to try to determine the reason for withdrawal. A letter detailing their desire to withdraw from the study may be requested by an investigator. For all participants lost to follow up, attempts to locate them will be documented.

Circumstances for which a patient would be determined as not continuing in the study:

- Completion/termination of study
- Death
- Concurrent illness
- Lost to follow-up
- Other

Investigators may also choose to withdraw participants if they are unable to continue participation in the study due to some condition unrelated to this study.

For all participants who withdraw from the study, a Study Completion Form will be completed.

Emergency Unblinding

Unbinding of participant treatment allocation may be required in the case of an adverse event. In such cases, if deemed necessary by the principal investigator, the participant's allocation may be revealed by the principal investigator, or a designee.

Modification of Protocol

Unless written approval from the applicable Ethics Committee has been obtained, there will be NO modifications made to this study protocol.

Any deviations to this study protocol will be detailed on a Protocol Deviation Form as soon as identified. Notification to the applicable Ethics Committee will be made according to the Ethics Committee requirements.

Definitions and Reporting of Adverse Events

Definitions

Adverse Events:

- Any undesirable clinical occurrence in a subject, whether it is considered to be study medication related or not, that includes a clinical sign, symptom, or condition; and/or an observation of an unintended technical procedural error.

Expected:

- An adverse event is expected when the specificity and severity of the event is consistent with a complication that is not related to the study specific medications or procedural technique, but may be related to the surgical procedure

Unexpected:

- An adverse event is unexpected when the specificity or severity of an adverse event is not consistent with the standard. It refers to an adverse event that has not been observed before

Adverse Study Medication Event:

- A clinical sign, symptom or condition that is causally related to the product, administration of the product, or performance of the product.

Serious Adverse Event:

- Any untoward medical occurrence that:
    - Results in death,
    - Is life threatening,
    - Requires inpatient hospitalisation or prolongation of hospitalisation,
    - Results in persistent or significant disability/incapacity,
    - May have caused a congenital anomaly/birth defect,
    - Requires intervention to prevent permanent impairment or damage,
    - Is a medically important event or reaction.

Reporting of Events

Adverse Events:

Any adverse event that occurs at any point in time from the beginning of the surgical procedure until either the participant is terminated from the study, or 7 days post-completion, should be recorded as follows:

- All information on general medical, operative, and study medication related complications (adverse events) will be documented on Case Report Forms.
- Information should include date of occurrence, description, severity, relationship to study medication, treatment, and date of resolution.
- The investigator will determine if the event is related to the study medication.
- Any adverse event in a study patient must be monitored until it has resolved or been considered non-clinically significant by the investigator.

Expected Events:

Should be reported to the principal investigator as soon as possible, but not later than five working days after the investigator first learns of the event

Adverse Study Medication Events

Study staff will ensure that any adverse study medication events which occur will be documented and immediately reported to the principal investigator. They should also be reported to the reviewing Ethics Committee and institution as soon as possible, no later than fifteen working days after the investigator learns of the event. An evaluation of the adverse events will be conducted by the investigator. Following this, if it is determined that the adverse effect presents an unreasonable risk to participants, the trial will be terminated as soon as possible. Termination shall occur no later than five working days after the investigator makes the determination, and no later than fifteen working days after the investigator first receives notice of the adverse event.

Serious Adverse Events (SAEs)

Any adverse event considered to be serious in nature which occurs at any time point from signing of Informed Consent Form until either the patient is terminated from the study, or 7 days post-completion, should be recorded as follows:

- All SAEs should be reported immediately to the principal investigator no later than 24 hours after becoming aware of the event.
- This will be followed promptly by detailed, written reports.

- The investigator should comply with the applicable regulatory requirement(s) related to the reporting of serious unexpected adverse study medication reactions to the regulatory authority (MedSafe NZ) and the Ethics Committee.
- All other SAEs not related to the study medication will be reported to the Ethics Committee as directed.

Ethics Committee

Approval

The investigator is responsible for obtaining Ethics Committee and Governance approval to conduct this study

Prior to Initiation of the Study

Written approval by the Ethics Committee and Governance must be obtained prior to beginning the study. Discussions may be had with prospective participants regarding the study, however written Patient Informed Consent must not be obtained. Until all approvals are granted, study procedures must also not be performed on prospective study participants.

Progress Reports

Progress reports on the trial will be submitted by the investigator at the request of the Ethics Committee.

Final Reports

Upon completion of the investigation, each investigator will submit an Ethics Close-Out Report on his/her part of the investigation within three months of completion of the investigation. This will be submitted to the Ethics Committee.

Use of Information and Publications

Investigators will and must respect data confidentiality. The information obtained during this study will be used in journals and conferences. Anonymity of the participants will be maintained.

Analysis/Conclusions

The data gathered in this investigation will be maintained and periodically assessed throughout the study. Given the above design and planned analysis, we believe this protocol is scientifically sound, and that clinical evaluation of the novel procedure is justified.

References

1. Li, J., Ma, Y. and Xiao, L., 2019. Postoperative Pain Management in Total Knee Arthroplasty. *Orthopaedic Surgery*, 11(5), pp.755-761.
2. Gaffney, C., Pelt, C., Gililland, J. and Peters, C., 2017. Perioperative Pain Management in Hip and Knee Arthroplasty.

   Orthopedic Clinics of North America, 48(4), pp.407-419.
3. Halawi, M., Vovos, T., Green, C., Wellman, S., Attarian, D. and Bolognesi, M., 2015. Opioid-Based Analgesia: Impact on Total Joint Arthroplasty. *The Journal of Arthroplasty*, 30(12), pp.2360-2363.
4. Luck, R., Haines, C. and Mull, C., 2010. Intraosseous Access. *The Journal of Emergency Medicine*, 39(4), pp.468-475.
5. Tobias, J. and Ross, A., 2010. Intraosseous Infusions: A Review for the Anesthesiologist with a Focus on Pediatric Use.

   Anesthesia & Analgesia, 110(2), pp.391-401.
6. Arthur, J., Bingham, J., Clarke, H., Spangehl, M. and Young, S., 2020. Intraosseous Regional Administration of Antibiotic Prophylaxis in Total Knee Arthroplasty. *JBJS Essential Surgical Techniques*, 10(4), pp.e20.00001.
7. Waisman, M., Roffman, M., Bursztein, S. and Heifetz, M., 1995. Intraosseous Regional Anesthesia as an Alternative to Intravenous Regional Anesthesia. *The Journal of Trauma: Injury, Infection, and Critical Care*, 39(6), pp.1153-1156.
8. Löser, B., Petzoldt, M., Löser, A., Bacon, D. and Goerig, M., 2019. Intravenous Regional Anesthesia: A Historical Overview and Clinical Review. *Journal of Anesthesia History*, 5(3), pp.99-108.
9. Young, S., Zhang, M., Freeman, J., Vince, K. and Coleman, B., 2013. Higher Cefazolin Concentrations with Intraosseous Regional Prophylaxis in TKA. *Clinical Orthopaedics & Related Research*, 471(1), pp.244-249.
10. Young, S., Zhang, M., Moore, G., Pitto, R., Clarke, H. and Spangehl, M., 2018. The John N. Insall Award: Higher Tissue Concentrations of Vancomycin Achieved With Intraosseous Regional Prophylaxis in Revision TKA: A Randomized Controlled Trial. *Clinical Orthopaedics & Related Research*, 476(1), pp.66-74.
11. Young, S., Zhang, M., Freeman, J., Mutu-Grigg, J., Pavlou, P. and Moore, G., 2014. The Mark Coventry Award: Higher Tissue Concentrations of Vancomycin With Low-dose Intraosseous Regional Versus Systemic Prophylaxis in TKA. *Clinical Orthopaedics & Related Research*, 472(1), pp.57-65.
12. Osafo, N., Agyare, C., Obiri, D. and Antwi, A., 2017. Mechanism of Action of Nonsteroidal Anti-Inflammatory Drugs.

    Nonsteroidal Anti-Inflammatory Drugs,.
13. Ghlichloo, I. and Gerriets, V., 2021. *Nonsteroidal Anti-inflammatory Drugs (NSAIDs)*. [online] Ncbi.nlm.nih.gov. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK547742/> [Accessed 30 June 2021].

14. Jankovic, R., Visnjic, M., Milic, D., Stojanovic, M., Djordjevic, D. and Pavlovic, M., 2008. Does the addition of ketorolac and dexamethasone to lidocaine intravenous regional anesthesia improve postoperative analgesia and tourniquet tolerance for ambulatory hand surgery?. *Minerva Anestesiol*, 74(10), pp.521-7.
15. Rivera, J., Villecco, D., Dehner, B., Burkard, J., Osborne, L. and Pellegrini, J., 2008. The efficacy of ketorolac as an adjunct to the Bier block for controlling postoperative pain following nontraumatic hand and wrist surgery. *AANA J*, 76(5), pp.341-5.
16. Jones, N. and Pugh, S., 1996. The addition of tenoxicam to prilocaine for intravenous regional anaesthesia. *Anaesthesia*, 51(5), pp.446-448.
17. Choyce, A. and Peng, P., 2002. A systematic review of adjuncts for intravenous regional anesthesia for surgical procedures. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie*, 49(1), pp.32-45.
18. Alfaro, R. and Davis, D., 2021. *Diclofenac*. [online] Ncbi.nlm.nih.gov. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK557879/> [Accessed 1 July 2021].
19. Gan, T., 2010. Diclofenac: an update on its mechanism of action and safety profile. *Current Medical Research and Opinion*, 26(7), pp.1715-1731.
20. MENDHAM, J. and MATHER, S., 1996. Comparison of diclofenac and tenoxicam for postoperative analgesia with and without fentanyl in children undergoing adenotonsillectomy or tonsillectomy. *Pediatric Anesthesia*, 6(6), pp.467-473.
21. Roelofse, J., van der Bijl, P. and Joubert, J., 1993. An open comparative study of the analgesic effects of tenoxicam and diclofenac sodium after third molar surgery. *Anaesthesia and Pain Control in Dentistry*, 2(4), pp.217-222.
22. Heinild, S., Søndergaard, T. and Tudvad, F., 1947. Bone marrow infusion in childhood. *The Journal of Pediatrics*, 30(4), pp.400-412.
23. Harper, K., Lambert, B., O'Dowd, J., Sullivan, T. and Incavo, S., 2020. Clinical outcome evaluation of intraosseous vancomycin in total knee arthroplasty. *Arthroplasty Today*, 6(2), pp.220-223.
24. Park, K., Chapleau, J., Sullivan, T., Clyburn, T. and Incavo, S., 2021. 2021 Chitranjan S. Ranawat Award: Intraosseous vancomycin reduces periprosthetic joint infection in primary total knee arthroplasty at 90-day follow-up. *The Bone & Joint Journal*, 103-B(6 Supple A), pp.13-17.
25. Atanda Jr, A. and Statter, M., 2008. Compartment syndrome of the leg after intraosseous infusion: guidelines for prevention, early detection, and treatment. *The American journal of orthopedics*, 37(12), pp.198-200.
26. Tobias, J. and Ross, A., 2010. Intraosseous Infusions: A Review for the Anesthesiologist with a Focus on Pediatric Use. *Anesthesia & Analgesia*, 110(2), pp.391-401.
27. Daniels, S., Melson, T., Hamilton, D., Lang, E. and Carr, D., 2013. Analgesic Efficacy and Safety of a Novel Injectable Formulation of Diclofenac Compared With Intravenous Ketorolac and Placebo After Orthopedic Surgery. *The Clinical Journal of Pain*, 29(8), pp.655-663.

28. Christensen, K., Daniels, S., Bandy, D., Ernst, C., Hamilton, D., Mermelstein, F., Wang, J. and Carr, D., 2011. A Double-Blind Placebo-Controlled Comparison of a Novel Formulation of Intravenous Diclofenac and Ketorolac for Postoperative Third Molar Extraction Pain. *Anesthesia Progress*, 58(2), pp.73-81.
29. Olsen, M., Bjerre, E., Hansen, M., Hilden, J., Landler, N., Tendal, B. and Hróbjartsson, A., 2017. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Medicine*, 15(1).
30. Laigaard, J., Pedersen, C., Rønsbo, T., Mathiesen, O. and Karlsen, A., 2021. Minimal clinically important differences in randomised clinical trials on pain management after total hip and knee arthroplasty: a systematic review. *British Journal of Anaesthesia*, 126(5), pp.1029-1037.
31. Lyman, S. et al., 2016. Validation of the Koos, Jr: A short-form knee arthroplasty outcomes survey. *Clinical Orthopaedics & Related Research*, 474(6), pp.1461–1471.
32. Huang, Y., Wang, C., Wang, C., Lin, W., Horng, L. and Jiang, C., 2008. Perioperative celecoxib administration for pain management after total knee arthroplasty – A randomized, controlled study. *BMC Musculoskeletal Disorders*, 9(1).
33. Danoff, J., Goel, R., Sutton, R., Maltenfort, M. and Austin, M., 2018. How Much Pain Is Significant? Defining the Minimal Clinically Important Difference for the Visual Analog Scale for Pain After Total Joint Arthroplasty. *The Journal of Arthroplasty*, 33(7), pp.S71-S75.e2.
34. Tubach, F., 2005. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Annals of the Rheumatic Diseases*, 64(1), pp.29-33.
35. Darnall, B., Sturgeon, J., Cook, K., Taub, C., Roy, A., Burns, J., Sullivan, M. and Mackey, S., 2017. Development and Validation of a Daily Pain Catastrophizing Scale. *The Journal of Pain*, 18(9), pp.1139-1149.

Appendix 1: Safety of the Intraosseous Route

The use of the intraosseous route for administration of both fluids and medications is well established. In 1947, Heinld [22] reported on the use of the intraosseous route in over 1000 paediatric patients, reporting a 95% success rate in administering fluids, blood products, and a variety of medications. The technique has been more popular in paediatric patients because intravenous access is more difficult; however intraosseous administration is equally as effective in adult patients.

The technique of intraosseous regional administration of antibiotics has been evaluated in humans in multiple randomised controlled trials [9, 10, 11]. No complications related to the use of the technique were found in these studies. Recent retrospective reviews involving large numbers of patients have shown that the IO route comes with minimal risk. Harper et al [23] reported no complications directly related to the IO insertion device out of 119 patients reviewed. Results from a study involving 488 patients in the IO group showed no cases of complications related to IO infusion [24].

The use of regional (with tourniquet inflated) intraosseous infusions of medications has also been investigated in humans. Waisman [7] investigated 109 patients who were given local anaesthetic agents through the regional intraosseous route, in both the upper and lower limbs, to allow surgical procedures to be performed on the limb with the patient awake. The procedure was successful in 106 of 109 patients, with 3 failures. In one patient the needle was incorrectly positioned, and two patients had inadequate anaesthesia which the authors attributed to an insufficient amount of medication infused. No other complications were reported. This paper is a useful reference as it has a very similar concept to our study (substituting the intraosseous route for intravenous in the regional delivery of medications) and provides evidence of the safety of the technique in a large number of patients.

IO access has potential risks. The inability to inject at the site indicates incorrect placement of the needle (not in the medullary space). Extravasation into soft tissues is the most common complication, commonly caused by cortical disruption from multiple attempts into the same site, dislodging of the needle into the soft tissues or misplacement. This may lead to other complications such as compartment syndrome, cellulitis, osteomyelitis, fat embolism, inability to remove IO needle. These complications are rare, with an overall incidence of <1% [4].

There are 4 main complications of intraosseous infusion that have been reported in adults. All relate to technical errors or prolonged infusions in an emergent setting, and are therefore extremely unlikely to occur in the single, controlled injection proposed in this study.

1) *Extravasation of fluid (due to incorrect needle placement)*

This complication occurs when a needle is not placed correctly (outside the bone), and infusion of fluid or medication is commenced. With modern intraosseous needles this complication is reduced by closely monitoring the patient, particularly at the IO needle insertion site, and using appropriate length IO needles to prevent over penetration through the bone. The reported success rates for the EZ-IO needle used in the current study range from 94-100%, and it is anticipated that as the needle will be placed by a trained orthopaedic surgeon in a controlled theatre environment the chance of incorrect needle placement will be very low.

2) *Compartment Syndrome*

Compartment syndrome again relates firstly to incorrect needle placement and has been described rarely in an isolated case report following intraosseous infusions [27]. It occurs if the tip of the needle is placed into soft tissues rather than bone, then prolonged infusion of fluids is commenced without recognition of the situation, leading to increased pressures within tissues. Llarge published series of intraosseous infusions have not reported this complication suggesting it is very rare [26]. It is extremely unlikely to occur in the context of this study as the needle is left in situ for a very short time, and fluid is injected as a single bolus so needle malposition or fluid leakage into the tissue will be immediately recognised.

3) *Fracture*

There have been isolated reports of fracture following intraosseous needle placement in the literature. This is thought to relate to the use of excessive force with manual needle placement, and to our knowledge has not been reported with the powered needle driver used in the current study.

4) *Infection / osteomyelitis*

A meta-analysis of 4359 intraosseous insertion attempts reported an incidence of infection of 0.6% [26]. It is anticipated that as the insertions in our study will take place in a fully sterile environment and antibiotic will be injected through the needle the incidence of infection is likely to be even lower.

The above complications will be outlined in the patient information sheet.

Appendix 2: NSAIDs and Voltaren™

Non-Steroidal Anti-Inflammatories

NSAIDs are antipyretic, anti-inflammatory, and analgesia agents, typically divided into groups based on their chemical structure and selectivity. Broadly they can be characterised into non-selective NSAIDs (COX-1 and COX-2) and COX-2 selective NSAIDs. NSAIDs mainly act by inhibiting the enzyme cyclooxygenase (COX) which is required in the production of prostaglandins and other eicosanoids, resulting in the mitigation of pain, fever, and inflammation [12, 13]. The two groups have slightly different side effect profiles due to their different selectivities.

The adverse effect profile of NSAIDs is well known and can affect multiple organ systems. Most importantly, COX-1 is heavily involved in maintaining gastric mucosal integrity and COX-2 is primarily involved in the process of inflammation. Theoretically, COX-2 inhibitors should provide the same anti-inflammatory effects while reducing gastric adverse effects [13]. Gastrointestinal (GI) side effects may include nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, GI ulcers, GI bleeding. Regarding cardiovascular events, all NSAIDs have an increased risk of hypertension, myocardial infarction, heart failure, stroke (and death). Other adverse effects include reduced renal perfusion and subsequent acute kidney injury, liver enzyme derangement (hepatotoxicity and hepatitis are rare consequences), and an increased risk of bleeding due to impaired platelet aggregation. As with any other medication, there is also the risk of anaphylaxis [12, 13]. Hence, it is desirable to avoid these systemic side effects, and regional administration allows us to do so by maximising local analgesia at the surgical site while minimising side effects.

Voltaren™ (Diclofenac)

Voltaren™ is the trade name for Diclofenac, indicated for use in the treatment and management of acute and chronic pain of various causes, and shares the analgesic, antipyretic and anti-inflammatory effects possessed by other NSAIDs. It is a non-selective NSAID, inhibiting both COX-1 and COX-2 with relative equipotency. However, there is evidence suggesting it has selective COX-2 inhibition from in-vitro experimentation, with around four times that of the inhibition of COX-2. Diclofenac is highly effective at inhibiting the production of PGE2, the primary prostanoid involved in inflammatory responses. Its analgesic action also appears to be due to the functional down-regulation of sensitised, peripheral pain receptors [18, 19].

Diclofenac shares a similar side effect profile to other drugs within the NSAID family, and this is due systemic exposure to the medication and the inhibition of COX enzymes (as mentioned prior). Even

though Diclofenac is a non-selective NSAID, because it appears to have slightly higher selectivity for COX-2 enzymes, it may have an advantage over other NSAIDs due to its relatively low GI toxicity, and potentially lower cardiovascular toxicity than COX-2 selective inhibitors, and minimal effects on renal and hepatic activity [19].

Utilisation of NSAIDs in IVRA (Bier's Block)

The use of NSAIDs as an adjuvant medication for IVRA has been extensively investigated. Jankovic et al [14] found that in patients undergoing hand surgery under IVRA, the use of 30 mg IV Ketorolac as an adjuvant to Lidocaine led to significantly lower intraoperative and postoperative pain visual analogue scores compared to patients without Ketorolac ($P < 0.001$). Another study involving 55 participants compared the efficacy of a Bier block using 50mL 0.5% Lidocaine plus 20 mg ketorolac compared to 50mL 0.5% lidocaine plus normal saline (placebo) in hand and wrist surgery. The Placebo group had significantly higher postoperative visual analogue scores at 30 minutes, 45 minutes, and 60 minutes [15]. In a study carried out by Jones et al [16], Tenoxicam was also found to be an effective adjunct to Prilocaine for IVRA compared to standard IVRA in Colles' fracture reduction. The parameters measuring this included a longer time before first additional analgesia was required, less total analgesic consumption, and lower pain scores. A systematic review of the evidence at the time suggested that NSAIDs had the most to offer as adjuvant medication to traditional IVRA regarding improving postoperative analgesia [17].

Other IV NSAIDs

Tenoxicam and Parecoxib are other anti-inflammatory medications used in the peri operative setting. Mendham et al [20] found that early pain scores in recovery for children undergoing adenotonsillectomy or tonsillectomy were significantly higher in the group receiving IV Tenoxicam (5.0; SD 2.63) than those being treated with rectal Diclofenac (3.0; SD 2.21, P=0.005). After the recovery period the pain scores for the Tenoxicam group were lower, however these findings were not significant. In another study, Roelofse et al [21] had similar findings, where patients who received Tenoxicam had significantly more pain for the first 3 hours following dental surgery compared to Diclofenac, then afterwards the pain scores did not differ. The evidence would suggest that Diclofenac is more effective in very early pain postoperative pain prevention but there is little difference in the early postoperative stages following this. Although an effective analgesic for postoperative pain relief, Parecoxib was not considered for this trial due to paucity of data on IO administration. It also needs to be converted to its active form, Valdecoxib, in the liver, meaning it would not be suitable for IORA given the use of a tourniquet to restrict surgical site circulation.