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Post-Operative Analgesia Following Total Knee Arthroplasty: A Randomized Controlled Trial Comparing Regional Techniques

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Abstract

Regional anaesthetic techniques for the management of post-operative pain following total knee arthroplasty (TKA) are becoming increasingly popular. The purpose of this randomized control trial was to assess whether periarticular infiltration and infusion (LIA and infusion) had a comparable time-to-discharge and analgesic quality to a motor-sparing nerve block (MSNB) technique in patients who have undergone TKA. The study arms included continuous MSNB (n=35, control) and LIA and infusion (n=35, experimental). Continuous anaesthetic infusion of 0.2% Ropivacaine was delivered at a rate of 8ml/hr post-operatively. The primary outcome was time to discharge. Secondary objectives included pain scores at rest and activity, narcotic consumption, patient satisfaction and functional outcomes. Preliminary analysis of 54 patients (MSNB n=29, LIA and infusion n=25) was performed. No significant differences in outcome measures were demonstrated between groups. Based on these early findings, LIA and infusion provides similar clinical and functional outcomes to MSNB following primary TKA.

Keywords

Total knee arthroplasty, primary, motor-sparing nerve block, periarticular infiltration, wound infusion, continuous regional anaesthesia

Lay Summary

Total knee replacement continues to become a more common surgical treatment option for knee arthritis in the Canadian population. Following surgery, a common complaint from patients is pain, which can inhibit their ability to mobilise early and delay discharge from hospital. Many pain options for pain control are available, each possessing their own benefits, but also potential risks. One promising option has been the use of local anaesthetic delivered around a nerve or the surgical site to decrease pain peripherally. This randomised trail assessed two pain control options using local anaesthetic that was constantly delivered either around a nerve or the surgical site to prolong the duration of pain control. These two groups were a motor-sparing nerve block (control group) and a novel periarticular infusion system (experimental group) that was placed in the tissue surrounding the knee joint. We compared the time to discharge, pain scores during rest and activity, narcotic medication consumption, and patient reported outcomes to assess if our experimental group produced similar outcomes to a proven peripheral nerve block following total knee arthroplasty. This study's purpose was to explore a continuous regional anaesthetic technique that was provided by a surgeon to circumvent factors such as resource constraints that prohibit the widespread use of peripheral nerve blocks in community centres for pain control following total knee replacement.

Co-Authorship Statement

This study was performed in collaboration with both members from the department of orthopaedic surgery as well as department of anaesthesia. Dr. James Howard MD, MSc, FRCSC assumed the role as primary investigator and supervisor, while orthopaedic surgery co-investigators were Dr. Edward Vasarhelyi MD, MSc, FRCSC and Dr. Brent Lanting MD, MSc, FRCSC. Anaesthesology co-investigators included Dr. Sugantha Ganapathy MD, FRCA, FRCPC, Dr. Mahesh Nagapa MD, FRCPC, Dr. Peter Mack MD, FRCPC, and Dr. Deepti Vissa MD. My responsibilities for this randomized control trial included protocol drafting for ethics committee consideration, patient screening, enrollment, data collection and final analysis. I authored this original thesis with the guidance of Dr. James Howard.

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Acronyms

ACB- Adductor canal block

ASA- American Society of Anaesthesiologists physical status classification system

BMI- Body mass index

FNB- Femoral nerve blocks

KSS- Knee Society Score

LIA- Local infiltration analgesia

MSNB- Motor-sparing nerve block

MVIC- maximum voluntary isometric contraction

NSAIDs- Non-steroidal anti-inflammatory drugs

OA- Osteoarthritis

PCA- Patient controlled analgesia

SF-12- Short-Form 12 Survey

SD- Standard deviation

SE- Standard error

TKA- Total knee arthroplasty

TUG-Timed up and go test

WOMAC- Western and McMaster Universities Osteoarthritis Index

Chapter 1

1 Introduction

The societal demand for total knee arthroplasty (TKA) in Canada is increasing as the population ages and average body mass index (BMI) grows, increasing from 55,501 cases in 2012 to 64,204 in 2016[1–4]. Though TKA has positive long-term functional outcomes and improved quality of life, the post-surgical pain associated with the procedure can affect patient's ability to perform physiotherapy effectively and negatively affect their post-operative satisfaction[5,6]. Pain is one of the most common post-operative complaints from patients and as it is a subjective experience, it can be challenging to anticipate and manage in the early post-operative period. Care-teams regularly rely on narcotic analgesics delivered through oral or intravenous patient-controlled analgesia (PCA) to reduce patients' pain, and though these are effective analgesic options, they have an undesirable side-effect profile[7]. These unwanted secondary effects are well documented, and range from nausea, sedation, pruritus, and constipation to more severe complications like addiction, respiratory depression, and death[8]. As a result, regional analgesic modalities have continued to pique the interest of the surgical community as effective alternatives to opioid-based management options. These include continuous epidural analgesia (CEA), femoral nerve blocks (FNB) and adductor canal block (ACB)/motor-sparing nerve block (MSNB), which have all been found to be effective in managing patient's immediate post-operative pain[9–12]. They also provide the option to deliver anaesthetic agents continuously for a longer analgesic duration, but each comes with varying adverse effects and logistical issues. CEA and FNB can cause quadriceps weakness and thus delay early mobilization, patient discharge, and increase the risk of inpatient falls[1013]. Motor sparing nerve blocks are increasing in popularity as they reduce the impact of most of these issues, but are expensive and require dedicated staff and resources, making it a challenge to implement as a standard care option in Canadian hospitals[14–16].

Another method that has been adopted in arthroplasty is the use of periarticular infiltration analgesia, where local anaesthetic is injected around the joint and incision to

provide thorough anaesthetic coverage[12,17]. Periarticular infiltration reduces the risk of a dense motor blockade following surgery and the resources required to provide regional blocks[12,18,19]. It also provides an analgesic quality comparable to that of regional blocks following TKA, but does not come without its own compromises[19–21]. A significant issue with periarticular infiltration is the inability to continuously deliver local anaesthetic after closure of the surgical incision. A previous study conducted in our center found that periarticular infiltration had a shorter analgesic duration compared to that of single-shot MSNB technique [12]. Without continuous infusion, increased narcotic consumption, inability to perform physiotherapy, and an increase in length of stay can occur after the duration of effective analgesia has passed.

We explored the application of periarticular infiltration and infusion, a regional anaesthetic method that allows for the continuous delivery of local anaesthetic following wound infiltration and closure. A feasible regional technique following TKA needs to manage pain to reduce narcotic consumption, be accessible to care providers, is cost-effective, and not inhibit patients' ability to ambulate so as to expedite discharge and reduce hospital resource utilization. By investigating time to discharge, pain, narcotic consumption, physiotherapy progress, and functional outcomes, we intend to determine if periarticular infiltration and continuous wound infusion is an effective regional anaesthetic alternative and is comparable in terms of analgesic quality and outcomes to our previously explored MSNB technique.

Chapter 2

2 Anatomy

2.1 Anatomy of the Thigh

2.1.1 Osteology

The femur makes up the skeletal structure in the thigh of the lower limb and is both the strongest and longest bone in the human body. It is part of the appendicular skeleton and articulates proximally with the acetabulum of the pelvis through the hip joint, a ball and socket type joint. Distally, the femur articulates with the proximal tibia through a modified hinge type joint called the tibiofemoral joint, as well as the patella through a gliding joint called the patellofemoral joint. Together, these create the knee joint. [22]

The structure of the femur is unique to suit its function as an essential load bearing structure and serves as the origin and insertion for 23 different muscles (figure 1). Proximally the major structures include the femoral head, neck, greater trochanter, lesser trochanter, intertrochanteric line, and gluteal tuberosity. The femoral head is a spheroidal structure that is oriented in an anterosuperiomedial direction off the femoral neck. Its smooth surface is only interrupted posteroinferiorly by the fovea, a roughened structure that allows for the insertion of the ligamentum teres. It is covered in articular cartilage and articulates with the acetabulum to create the hip joint. The femoral neck projects from the femur at an average neck-shaft angle of 135 degrees, with an anteversion angle of 15-20 degrees. At its base is where the greater and lesser trochanters can be found. The greater trochanter is found posterolateral and serves as the attachment for multiple muscle groups. Gluteus minimus and gluteus medius insert at the greater trochanter to provide the action of hip abduction. The lesser trochanter can be found posteroinferiorly at the junction of the femoral shaft and the base of the femoral neck and serves as the tendinous insertion point for the iliacus and psoas muscles responsible for hip flexion. The intertrochanteric line is a ridge of bone found anteriorly on the femur at the junction of the femoral neck and shaft. Structures that

attach to it include the lateral border of the hip joint capsule as well as the iliofemoral ligament. [22]

The diaphysis of the femur is the long, cylindrical shaped portion and has an anterior bow with a femoral radius of curvature ranging from 98-120cm in the sagittal plane [23]. The diaphysis extends distally at an oblique angle to allowing for a weight bearing axis that travels through the centre of the femoral head, knee joint and ultimately ankle joint. Posteriorly, along its shaft, runs a roughened line called the linea aspera, which serves as the insertion point for medial compartment adductors as well as the vastus medialis and lateralis, short head of biceps femoris and a portion of the gluteus maximus at the gluteal tuberosity of the linea aspera. As the diaphysis travels distally, the femoral shaft begins to flare and form the lateral and medial condyles that articulate with the proximal tibia as well as the medial and lateral epicondyles and adductor tubercle which serve as the attachment points for various ligaments and tendons. Between the two condyles you will find the trochlear groove, a smooth area that makes up the femoral portion of the patellofemoral joint.

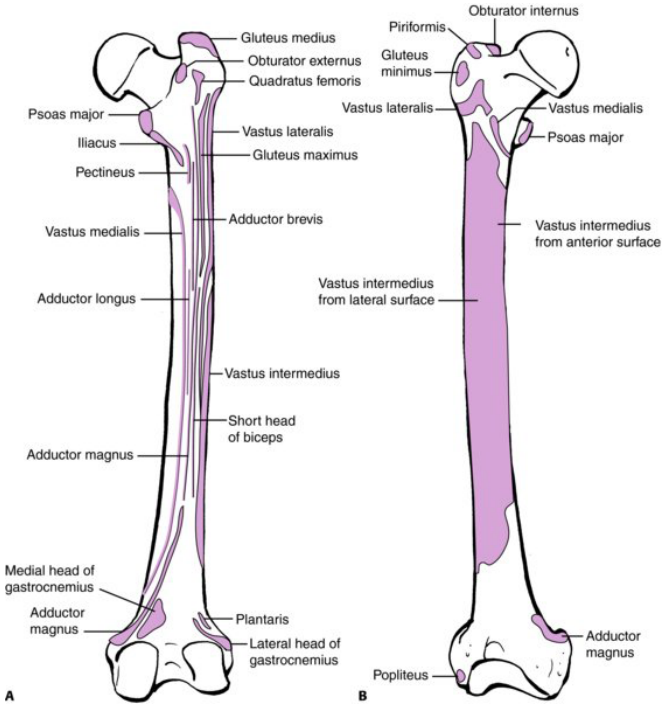

Figure 1: Posterior (A.) and anterior (B.) femoral muscular attachments

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2.1.2 Muscular Compartments:

The thigh is divided into three osteofascial compartments, called the anterior, posterior and medial compartments of the thigh. Two Intermuscular fascial septa extend from the fascia lata, the tough deep fascia of the thigh, down to the bone forming the anterior and posterior osteofascial compartments. The medial compartment is functionally considered its own compartment, as it is not separated by a distinct fascial plane. Figure 2 demonstrates their various attachments and insertions. [22]

2.1.2.1 Anterior Compartment:

The anterior compartment is most functionally involved with knee joint extension, but also hip flexion. The muscles contained in the anterior compartment include sartorius, rectus femoris, vastus medialis, vastus medialis obliquus, vastus lateralis, vastus intermedius, and articularis genu. The muscles rectus femoris, vastus medialis, vastus lateralis, and vastus intermedius are collectively referred to as quadriceps femoris[22]. Table.1 provides information regarding origin, insertion, action, innervation, and vascular supply for the anterior compartment muscles.

Table 1: Anterior compartment muscles

Muscle	Origin	Insertion	Action	Innervation	Vascular Supply
Sartorius	Anterior Superior Iliac Spine	Pes Anserinus	Knee extension, hip flexion, thigh abduction and internal rotation	Femoral Nerve (L2-3)	Branches from Superficial Femoral Artery
Rectus Femoris	Anterior inferior iliac Spine and groove superior to acetabulum	Quadriceps femoris tendon-> patella	Knee extension	Femoral Nerve (L2-4)	Artery of the Quadriceps
Vastus Medialis	Inferior aspect Intertrochanteric	Quadriceps femoris	Knee extension	Femoral Nerve (L2-4)	Branches from

	line, medial lip of linea aspera, medial supracondylar line, medial intermuscular septum	tendon-> patella			Superficial Femoral Artery
Vastus Medialis Obliquus	Lowest fibres of Vastus Medialis (same intsertion)	Quadriceps femoris tendon-> patella	Patellofemoral joint stability	Femoral Nerve (L2-4)	Artery of the Quadriceps
Vastus Lateralis	Superior aspect Intertrochanteric line, anterior and inferior borders of greater trochanter, lateral lip of gluteal tuberosity, lateral lip of linea aspera	Quadriceps femoris tendon-> patella	Knee extension	Femoral Nerve (L2-4)	Artery of the Quadriceps
Vastus Intermedius	Anterior and lateral upper two-thirds of femoral shaft, lateral intermuscular septum	Quadriceps femoris tendon-> patella	Knee extension	Femoral Nerve (L2-4)	Artery of the Quadriceps
Articularius Genu	Distal anterior femoral shaft	Proximal reflection of knee joint synovium	Pulls suprapatellar bursae during knee extension	Femoral Nerve (L2-4)	Lateral Femoral Circumflex Artery

2.1.2.2 Medial Compartment:

The medial compartment is responsible for adduction across the hip joint, and thus the lower leg. Some muscles have multiple compartments, having portions in the medial compartment as well as the anterior or posterior compartments. These include adductor magnus (medial and posterior compartments), adductor longus (medial and anterior

compartments) and pectineus (medial and anterior compartments). Though the medial compartment is not defined by intermuscular fascial septae, it is functionally considered a separate osteofacial compartment[22]. Table 2 provides information regarding origin, insertion, action, innervation, and vascular supply for the medial compartment muscles.

Table 2: Medial compartment muscles

Muscle	Origin	Insertion	Action	Innervation	Vascular Supply
Pectineus	Pecten pubis	Lesser trochanter and linea aspera	Hip adduction and flexion	Femoral (L2-3) nerve +/- accessory obturator nerve (L3)	Medial femoral circumflex artery
Gracilis	Inferior pubic ramus	Pes anserinus	Hip adduction, flexion and medial rotation	Obturator nerve (L2-3)	Artery to the adductors branch of profunda femoris
Adductor Longus	Pubic body, below pubic crest	Linea aspera	Hip adduction and gait stabilization	Obturator nerve (L2-4)	Artery to the adductors branch of profunda femoris
Adductor Brevis	Inferior pubic ramus	Lesser trochanter and linea aspera	Hip adduction and gait stabilization	Obturator nerve (L2-3)	Artery to the adductors branch of profunda femoris
Adductor Magnus	Inferior pubic ramus, ischial ramus, and ischial tuberosity	Linea aspera and adductor tubercle	Hip adduction and gait stabilization	Obturator nerve and sciatic nerve (L2-4)	Branches of the profunda, obturator, and superficial femoral arteries

Within the medial compartment, a triangular shaped canal called the adductor canal is formed by the borders of sartorius anteriorly, vastus medialis anterolaterally, and posteromedially by adductor longus and magnus (figure 2). Commonly referred to as the adductor canal, it is also known as Hunter's canal or the sub-sartorial canal, and contains the femoral artery and vein, descending genicular and muscular branches of the femoral artery, the saphenous nerve, and the nerve to vastus medialis prior to its insertion into the muscle. The adductor canal begins at the apex of where the medial margins of sartorius and adductor longus meet. Two-thirds of the way down the canal the femoral vessels pass posteriorly into the popliteal fossa through the adductor hiatus, an tendinous opening in adductor magnus [2224].

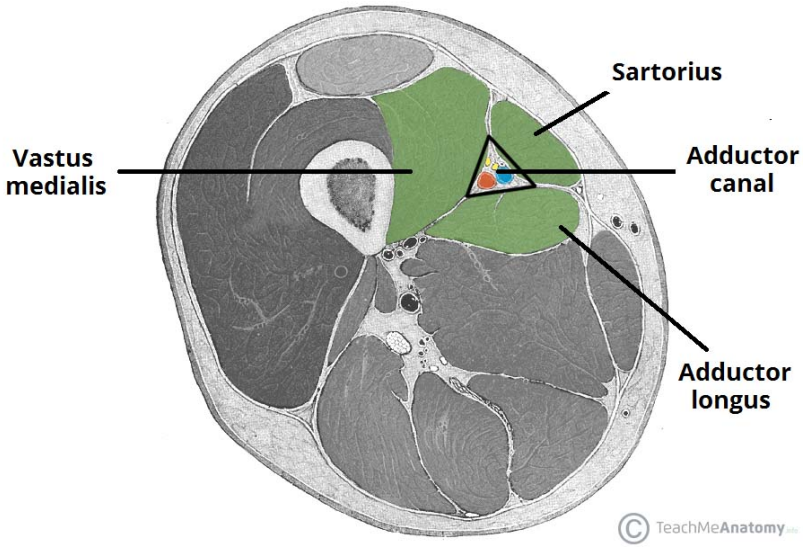

Figure 2: The borders of the adductor canal

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2.1.2.3 Posterior Compartment:

The posterior compartment of the thigh has the function of knee flexion and hip extension and include the following muscles; biceps femoris, semitendinosus, and semimembranosus. Collectively known as the hamstring muscles, they span across both the knee and hip joints. At the knee, they form the proximal borders of the popliteal

fossa, with the biceps femoris laterally and semimembranosus and semitendinosus medially. Table 3 provides information regarding origin, insertion, action, innervation, and vascular supply for the posterior compartment muscles

Table 3: Posterior compartment muscles

Muscle	Origin	Insertion	Action	Innervation	Vascular Supply
Biceps Femoris	Long head- ischial tuberosity, sacrotuberous ligament Short head- lateral lip of linea aspera	Head of the fibula, fibular collateral ligament, and lateral tibial condyle	Hip extension, knee flexion, and lateral rotation of thigh	Sciatic nerve (L5, S1-2)	Perforating branches of profunda femoris, medial
Semitendinosus	Ischial tuberosity- inferomedially	Pes anserinus	Hip extension and knee flexion	Sciatic nerve (L5, S1-2)	Perforating branches of profunda femoris
Semimembranosus	Ischial tuberosity- superolaterally	Medial tibial condyle.	Hip extension and knee flexion	Sciatic nerve (L5, S1-2)	Perforating branches of profunda femoris

2.1.3 Muscle and Cutaneous Innervation:

The lumbar and sacral plexuses are responsible for providing the lower limb both motor and sensory functions through a number of nerve branches. The lumbar plexus leaves the spinal canal at vertebral levels L1-L3 and travels deep within the psoas major muscle, while the lumbosacral trunk (L4-L5) travels medial on the posterior abdominal wall. The sacral plexus (S1-4) travels within the pelvis on the anterior surface of the piriformis muscle and external to the pelvic fascia. Together, the lumbosacral trunk and sacral plexus form the lumbosacral plexus. These collections of nerve roots form their associated branches the more distal they move[22]. The primary segmental innervation associated with various hip and knee movements can be found in table 4.

Table 4: Segmental innervation and principle nerve roots for hip and knee movement

Movement	Muscle Group	Nerve	Root
Hip Flexion	Iliopsoas	Femoral Nerve	L1-2
Hip Extension	Gluteus maximus	Sciatic Nerve	L5-S1
Hip Abduction	Gluteus medius and minimus, Tensor Fasciae Latae,	Superior Gluteal Nerve	L4-L5
Hip Adduction	Adductors	Obturator Nerve	L2-3
Knee Flexion	Hamstring Muscles	Sciatic Nerve	S1
Knee Extension	Quadriceps femoris	Femoral Nerve	L3-4

2.1.3.1 Lateral Cutaneous Femoral Nerve (L2-3):

The lateral cutaneous femoral nerve arises at the spinal levels of L2-3. Its route to the thigh begins at the lateral boarder of the psoas major muscle, crossing the iliacus muscle and entering the leg medial to the anterior superior iliac spine either through or posterior to the inguinal ligament. From there, the nerve will variably pass through or behind sartorius where two branches arise, the anterior and posterior divisions. The anterior supplies sensory innervation to the anterolateral thigh as far as the knee. The posterior is responsible for the skin overlying the greater trochanter and may supply some of the gluteal area[22].

2.1.3.2 Femoral Nerve (L2-4):

The femoral nerve is primarily responsible for the anterior compartment of the thigh. It provides motor innervation for muscles involved in knee extension and hip flexion as well as cutaneous sensory branches. It is the largest branch of the lumbar plexus and gives innervation to the iliacus and pectineus before dividing into the anterior and posterior femoral nerve branches at the level of the lateral femoral circumflex artery. The anterior division of the femoral nerve supplies the medial and intermediate cutaneous nerves of the thigh (figure 3) as well as the nerve to sartorius. The posterior

division contains the motor branches to quadriceps femoris (rectus femoris, vastus medialis, vastus medialis obliquus, vastus lateralis, vastus intermedius) as well as the largest and longest femoral nerve cutaneous branch, the saphenous nerve. The saphenous nerve is responsible for sensation to the medial aspect of the knee as well as the lower leg. It descends through the adductor canal and at the distal end gives off an infrapatellar branch (contributes to the peripatellar plexus) providing sensation to the anteromedial capsule, and patellar tendon. It then pierces the fascia lata between the tendons of gracilis and sartorius and continues subcutaneously to supply the prepatellar skin and medial lower leg, accompanying the long saphenous vein.

2.1.3.3 Obturator Nerve (L2-4):

The obturator nerve originates from the lumbar plexus at roots L2-4. It descends within the psoas major muscle, passing behind the common iliac vessels, along the lateral wall of the pelvis and to the obturator foremen. At the foremen, it divides into the anterior and posterior branches, with the anterior providing motor function to adductor longus, gracilis, and usually adductor brevis and pectineus as well. It also provides sensory input from the hip joint as well as a cutaneous branch that contributes to the subsartorial plexus, a network of sensory nerves for the medial aspect of the thigh. The posterior branch provides adductor magnus with its motor input as well as adductor brevis (when not supplied by the anterior branch). Its terminal branch is the genicular branch of the obturator nerve, a sensory filament for the knee joint capsule within the popliteal fossa.

2.1.3.4 Sciatic Nerve (L4-5, S1-3):

The sciatic nerve is the thickest nerve in the body and has plexus contributions from both the lumbosacral trunks (L4-L5) and sacral plexus (S1-3). It exits the pelvis through the greater sciatic foramen, below the piriformis muscle, and descends distally deep to gluteus maximus along the posterior aspect of the thigh. Along its path, it provides sensory branches to the posterior capsule of the hip joint, as well as motor branches to the biceps femoris, semitendinosus, semimembranosus, and the ischial origin of adductor magnus. Proximal to the knee, it branches into its two largest components, the

tibial and common peroneal nerves. Though the level of division is highly variable, it is typically described to occur at the junction of the middle and distal thirds of the thigh. The tibial nerve is responsible for innervating the deep and superficial posterior compartments of the lower leg, and the common peroneal nerve innervates the lateral and anterior compartments through its superficial and deep branches respectively[22].

2.1.3.5 Posterior Cutaneous Nerve of the Thigh (S1-3):

The posterior cutaneous nerve stems from the sacral nerve roots S1-3 and leaves the pelvis through the greater sciatic foremen. It travels distally beneath the fascia lata in the thigh and superficial to the long head of biceps femoris, providing sensory input from the gluteal, perineum, and posterior thigh and knee.

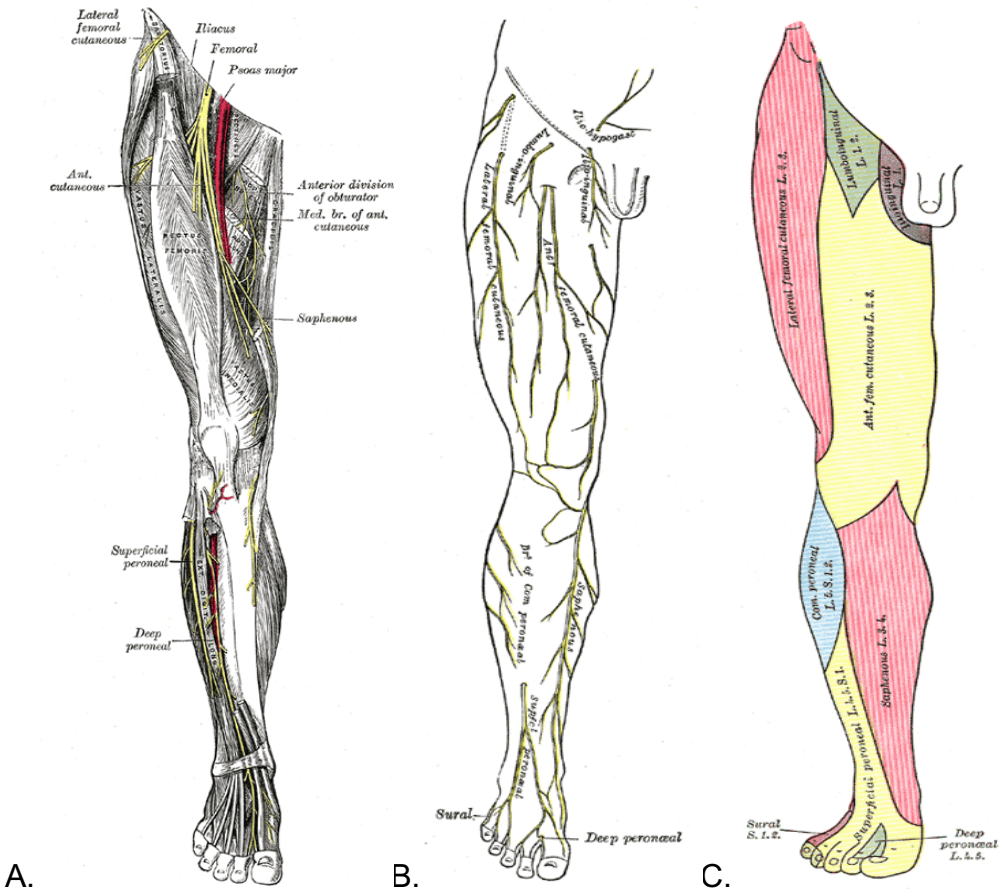

Figure 3: The nerves (A.), cutaneous branches (B.) and segmental cutaneous distribution (C.) of the lower limb

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2.2 Arterial Blood Supply:

The blood supply for the thigh is provided by the femoral artery and its associated branches. The femoral artery is a branch of the external iliac artery, and begins at the mid-inguinal point, an anatomical landmark found halfway between the pubic symphysis and anterior superior iliac spine. It descends through the anteromedial aspect of the thigh through the adductor canal and distally goes posterior through the adductor hiatus to become the popliteal artery. In the proximal thigh the femoral artery is referred to as the common femoral artery and its branches include the superficial epigastric artery, superficial circumflex iliac artery, superficial external pudendal artery, deep external pudendal artery, and the profunda femoris. Distal to the profunda femoris, the common femoral artery becomes the superficial femoral artery and provides muscular branches to sartorius, vastus medialis, the adductors, as well as the descending genicular artery branch. The profunda femoris supplies the hip joint as well as muscles in all three osteofascial compartments. Branches include the lateral and medial circumflex femoral arteries, four perforating arteries (terminal profunda is the forth) as well as muscular branches to the adductors and posterior compartment muscles[22].

2.3 Anatomy of the Knee Joint:

2.3.1 Osteology:

The knee is a modified hinge type synovial joint that has two articulations, the tibiofemoral joint and patellofemoral joint. The three bones that make up these joints are the femur, tibia, and patella.

The tibiofemoral joint is the articulation point between the distal femur and proximal tibia. The joint surfaces are made up of the convex surfaces of medial and lateral condyles of the distal femur which are in contact with the articular facets on the medial and lateral condyles of the tibial plateau. Their surfaces are covered in a layer of articular cartilage to allow smooth, low friction movement[25].

Distally on the femur, the lateral epicondyle serves as the origin on the lateral collateral ligament, while the medial epicondyle is the same for the medial collateral ligament. The trochlear groove is a depression anteriorly on the femur that stabilizes the patella in the patellofemoral joint during range of motion. Inferiorly and posteriorly is an area called the intercondylar fossa where the anterior and posterior cruciate ligaments are found. The tibial plateau slopes posteriorly and downwards in relation to the tibial shaft and is where the intercondylar eminence or tibial spine is found. Two prominences can be found here, the medial and lateral intercondylar tubercles, anterior to which the anterior horns of the medial and lateral menisci insert as well as the anterior cruciate ligament. Posterior to the tubercles, the posterior horns of the menisci and posterior cruciate ligament insert onto the tibia. Inferior to the joint line, and on the anterior aspect of the tibia, is where the tibial tuberosity is found and is the insertion point for the patellar tendon. Lateral and superior to this area, another prominence called Gerdy's tubercle serves as the insertion site for the Iliotibial tract[2225].

The patella is the largest sesamoid bone in the human body and is encapsulated by the quadriceps tendon. With flexion and extension, the patella articulates with the distal femur in the trochlear groove. Posteriorly on the patella, different areas are in contact with the femur during the knee joint's range of movement. The upper medial and lateral facets are in contact with the femur during flexion, the lower medial and lateral facets during extension, and the medial vertical facet during extreme flexion[25].

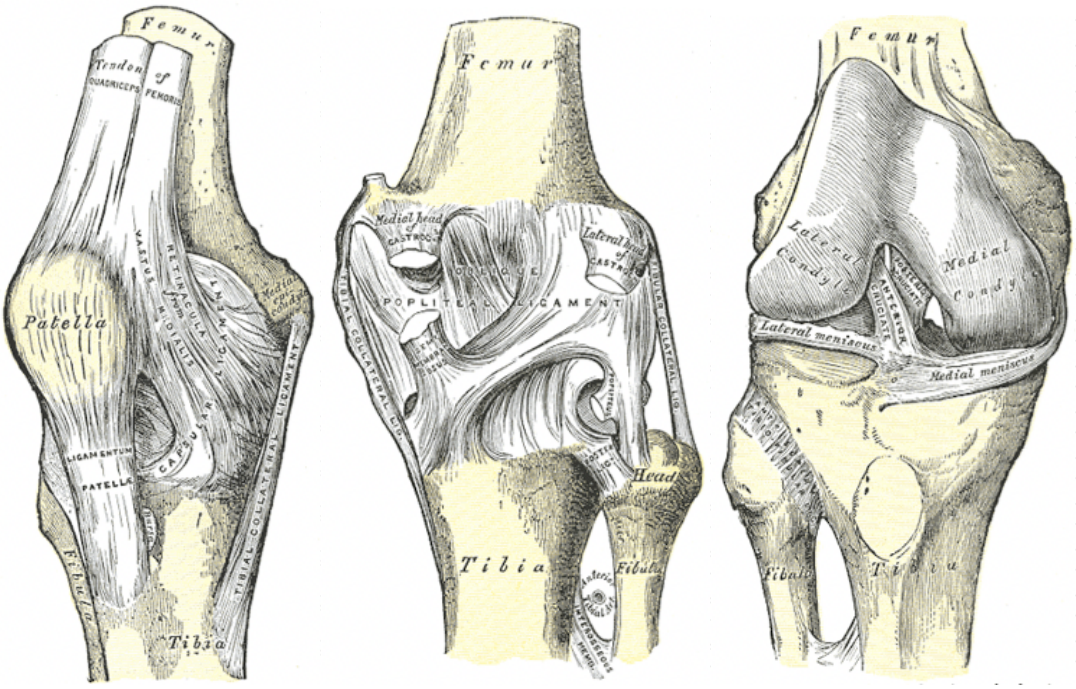

Figure 4: The knee joint

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2.3.2 Muscles and Popliteal Fossa:

The muscles responsible for knee joint movement are found in table 5.

Table 5: Muscles responsible for knee movement

Movement	Muscles
Knee Flexion	Biceps femoris, semimembranosus, semitendinosus (assisted by gracilis, sartorius, gastrocnemius, and plantaris)
Knee Extension	Rectus femoris, vastus lateralis, vastus medialis, vastus intermedius
Medial Rotation (flexed leg)	Popliteus, semimembranosus, semitendinosus (assisted by sartorius and gracilis)
Lateral Rotation (flexed leg)	Biceps femoris

A unique muscle to the knee joint is the popliteus. Popliteus is innervated by the tibial nerve (L4-5, S1) and forms the floor of the popliteal fossa and is intracapsular, but extra-synovial to the knee joint. Its origin is the lateral aspect of the lateral femoral condyle and inserts on the posterior surface of the tibia, proximal to the soleus line. Its function is to rotate the tibia medially or the femur laterally to unlock a fully extended knee at the beginning of flexion[22].

Posteriorly, the hamstring and medial and lateral heads of gastrocnemius form the borders of the popliteal fossa. The popliteal fossa has a diamond shape, and its borders laterally are the biceps femoris proximally and the lateral head of gastrocnemius distally. Medially, semimembranosus and semitendinosus are the proximal medial border, while the medial head of gastrocnemius makes up the distal medial border. The floor (anterior boundary) is made up of the posterior aspect of the femur, the oblique popliteal ligament, posterior capsule of the knee joint, and popliteus with its associated overlying facia. The roof (posterior boundary) is the popliteal facia. The contents of the popliteal fossa include the common peroneal and tibial nerves (most superficial structure), sural nerve, short saphenous vein, popliteal lymph nodes, posterior cutaneous nerve of the thigh, genicular branch of the obturator nerve, fat, and the popliteal vein and artery (deepest structure).

2.3.3 Ligaments:

There are four major ligaments that stabilize the knee joint in different planes, the anterior and posterior cruciate and medial and lateral collateral ligaments. The anterior cruciate ligament (ACL) is responsible for restricting anterior movement of the tibia in relation to the distal femur. It originates on the posteromedial aspect of the lateral femoral condyle and distally inserts anterolaterally to the medial tibial eminence, blending with the anterior horn of the lateral meniscus. The posterior cruciate ligament (PCL), resists posterior translation of the tibia in relation to the distal femur, and is thicker and stronger than the ACL. It originates from the lateral aspect of the medial

femoral condyle and extends to the roof of the intercondylar notch. Crossing posterior to the ACL, it distally inserts onto the posterior tibia in the intercondylar region[22,25].

The medial collateral ligament is attached to the medial epicondyle of the distal femur, and resists valgus producing forces on the knee joint. Its deep fibres are attached to the medial meniscus and distally inserts onto the medial condyle and body surface of the tibia, approximately 2.5cm distal to the condyle. On the lateral aspect of the knee joint, the lateral collateral ligament works to resist varus producing forces and is attached to the lateral femoral epicondyle. Its insertion distally is on the fibular head, and in contrast to the MCL, is not adherent to the lateral meniscus as it descends.

2.3.4 Meniscus:

The medial and lateral menisci of the knee are fibrocartilaginous structures that increase tibiofemoral congruency, act as a secondary stabilizer for the knee joint, minimize tibiofemoral contact pressure, and contribute to joint lubrication and articular cartilage nutrition [25]. These crescent shaped intracapsular structures are poorly vascularized and cover approximately two thirds of their associated articular surfaces. Each possess an anterior and posterior horn, highly innervated areas compared to the rest of the meniscus that provide attachment points centrally on the tibia. The medial meniscus is semi-circular in shape and its anterior horn is attached anterior to the insertion site of the ACL in the intercondylar area of the tibial plateau. Its posterior horn also attaches to the tibia in the intercondylar area, though its insertion is more posterior between the insertion of the PCL and the posterior horn of the lateral meniscus. Unlike the lateral meniscus, the medial meniscus is also adherent to the joint capsule peripherally as was all the deep fibers of the MCL. The shape of the lateral meniscus is nearly a full circle, and its anterior horn inserts posterolateral to the ACL insertion and its fibers blends into it. The posterior horn insertion is found between the tibial eminence and the posterior horn insertion of the medial meniscus and uniquely uses meniscofemoral ligaments attached to the medial femoral condyle to anchor its position[25].

2.3.5 Capsule and Synovium:

The knee joint capsule is a tough fibrous layer surrounds the knee joint. Its margins anteriorly include the patella and the patellar tendon. The capsule extends posteriorly to the collateral ligaments and distally to the condyles of the tibia. The posterior boundaries are the articular margins of the femoral condyles, intercondylar notch, and posterior proximal tibia. The synovial membrane is a unique tissue that lies deep to the capsule on the knee. Its function is the production of synovial fluid that lubricates the tibiofemoral and patellofemoral joints during flexion and extension. Its insertion is along the articular margins of the patella, femur and tibia and forms a large suprapatellar bursa between the quadriceps tendon and the distal femur[22].

2.3.6 Cutaneous and Articular Innervation:

The peripatellar plexus is a network of nerves responsible for sensation over and around the patella. It arises from connections between the infrapatellar branch of the saphenous nerve as it travels medial to anterior, medial femoral cutaneous nerve, intermediate femoral cutaneous nerve, and the lateral femoral cutaneous nerve. Figure 5 displays the cutaneous distribution around the knee joint. The Intermediate femoral cutaneous nerve provides anterior coverage, the saphenous nerve anteromedial, the lateral sural cutaneous nerve laterally and the posterior cutaneous nerve of the thigh for sensation posteriorly.

The articular innervation is through genicular branches from the obturator, femoral, tibial, and common peroneal nerves. The posterior aspect is supplied by the genicular branch of the obturator nerve, a terminal division of the posterior branch of the obturator nerve. The femoral nerve branches to vastus medialis terminate as articular sensory branches at the knee joint. The tibial nerve provides genicular branches that run with

the medial and middle genicular arteries, and the common peroneal sends branches that run with the lateral genicular artery as well as the anterior tibial recurrent artery[22].

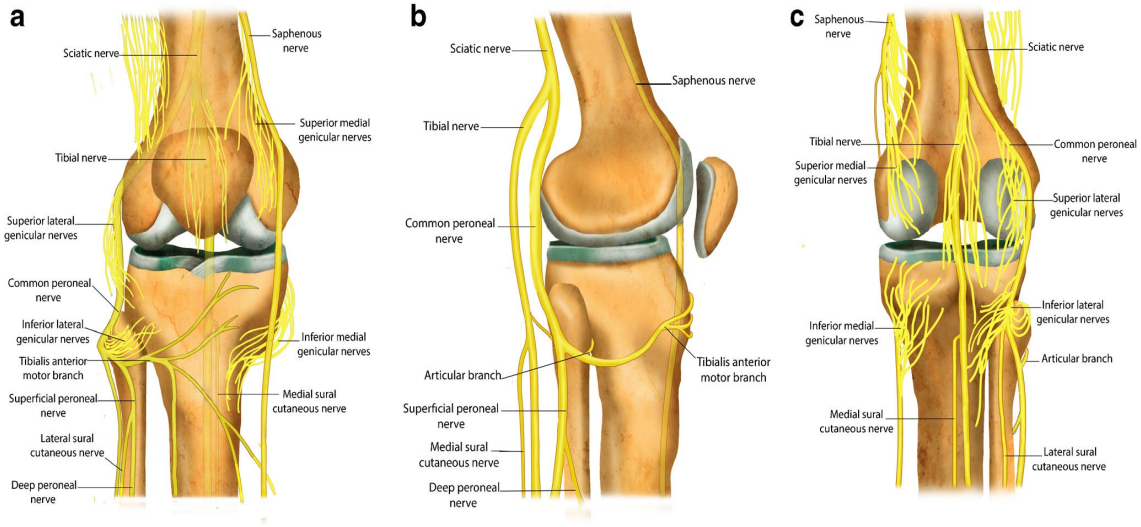

Figure 5: Knee joint articular innervation from anterior (A.), lateral (B.), and posterior (C.)

Reprinted with permission by [26] Goldman DT, Piechowiak R, Nissman D, Bagla S, Isaacson A. Current Concepts and Future Directions of Minimally Invasive Treatment for Knee Pain. Curr Rheumatol Rep. 2018;20(9).

2.3.7 Blood Supply:

The arterial anastomosis surrounding the knee joint receives contribution through a number of genicular branches of the popliteal, superficial femoral, lateral circumflex femoral, posterior and anterior tibial arteries[22]. There are superior, middle and inferior genicular artery branches arising from each of these larger vessels (figure 6). The medial and lateral (deep and superficial) superior genicular branches come from the popliteal artery, and curve around the femoral condyles anteriorly to supply the front of the knee. The descending genicular artery, a branch of the superficial femoral artery, anastomosis with the medial superior genicular artery. Further arterial connections occur between the medial superior genicular artery and the inferior medial genicular artery as well as the deep branch of the lateral superior genicular artery. The superficial

lateral superior genicular artery anastomosis with the descending branch of the lateral circumflex femoral artery as well as the inferior lateral genicular artery. The middle genicular artery also stems from the popliteal artery and is responsible for the cruciate ligament and synovial membrane blood supply. The medial and lateral inferior genicular arteries arise from the popliteal artery as well. The lateral inferior genicular anastomoses with the lateral superior, medial inferior, anterior and posterior recurrent tibial arteries (branches of the anterior tibial artery), and circumflex fibular artery (branch of the posterior tibial artery). Together, this complex network of vessels supply the knee joint with arterial blood[22].

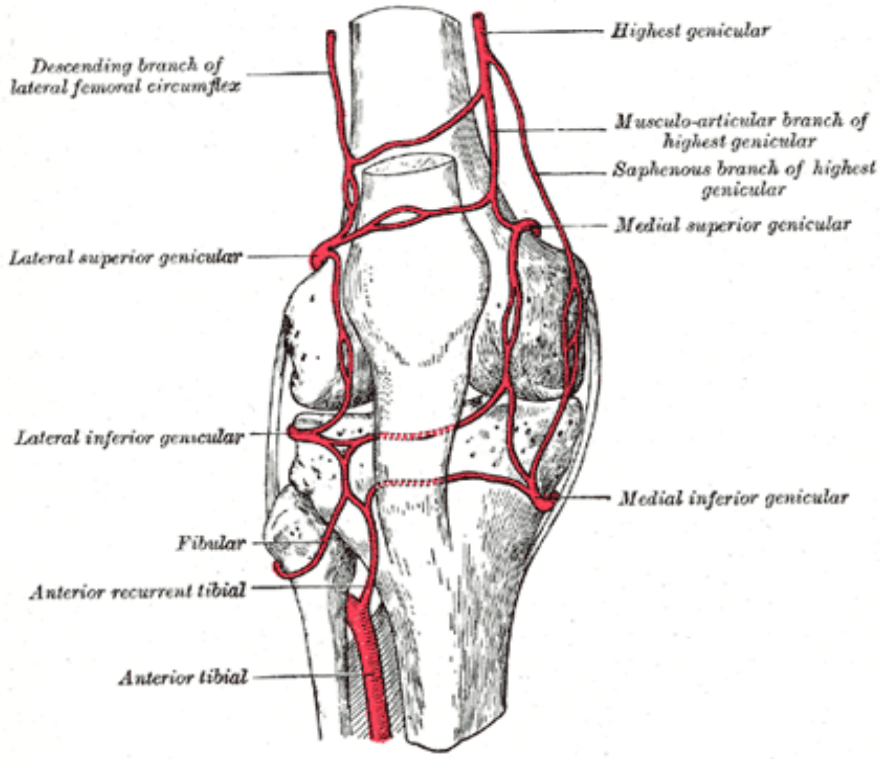

Figure 6: Arterial anastomosis of the knee joint

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Chapter 3

3 Literature Review

3.1 Knee Joint Arthritis:

Arthritis occurs when there is a medical or structural condition that is promoting inflammation within the joint. There are over 100 different diseases that cause arthritis through a variety of pathophysiologic pathways that lead to localized bone and articular cartilage destruction [27]. Common etiologies include rheumatoid arthritis, seronegative spondyloarthropathies [28], osteoarthritis, and post-traumatic. Though the pathological process is different depending on the underlying cause, arthritic diseases share similar symptoms and signs including joint pain, joint swelling, erythema, stiffness, loss of range of movement, decreased function and significant disability.

In Canada, arthritis as a whole is the most prevalent chronic health condition that affects 1 in 5 people over the age of 15, and 1 in 2 seniors over the age of 65 [27]. It has a female predominance with 59.5% of sufferers being women [27]. The total economic burden arthritis places on the Canadian economy was estimated to be 6.1 billion dollars in the year 2000, 33 billion dollars in 2010 and is projected to be 67 billion dollars by 2031. This steady rise is primarily due to the aging population and rising incidence of obesity as both are strong risk factors for arthritis[29,30]. In the knee, the most common arthritic conditions are osteoarthritis, rheumatoid arthritis, and post-traumatic arthritis (secondary osteoarthritis) [31,32]

3.2 Knee Osteoarthritis:

Also known as degenerative arthritis or degenerative joint disease, osteoarthritis (OA) is a condition characterized by articular cartilage deterioration and sclerosis of the underlying bone [33,34].

The knee is the most common site for osteoarthritis followed by the hand and hip joints[35–37]. The age and sex standardized incidence of knee osteoarthritis is 240/100000

with the annual incidence in Canada expected to rise from e [30,35,38]. Knee OA accounts for approximately 80% of the overall osteoarthritis disease burden[39]. Being the most common arthritic condition affecting the knee joint, in 2016, primary total knee arthroplasty was performed for a diagnosis of OA in 98.8% (n=46,241) of cases in Canada[40]. Because of this, knee OA carries a significant economic and public health burden.

The exact etiology of osteoarthritis can be difficult to determine, but the overlying diagnosis is divided into two separate types, primary and secondary. Primary or idiopathic OA is associated with aging and said to have occurred when there is no identifiable initiating event or major risk factors such as previous trauma or obesity[34,41]. As articular cartilage ages, imbalances in chondrocyte metabolic pathways and changes in the extra-cellular matrix occur as a result of a number of fundamental biologic processes[42,43]. These include increased matrix degradation, reduced matrix repair, increased cell death, chondrocyte hypertrophy, calcification and crystallization, subchondral sclerosis, osteophyte formation, focal bone remodeling and synovitis [41]. These age-related changes are responsible for the major pathologic features of OA which consist of articular cartilage degradation, ligament and meniscus degradation, subchondral sclerosis, osteophyte formation, and joint capsule hypertrophy [41]. Secondary osteoarthritis occurs as a result of a precipitating factor such as previous injury to articular surface, meniscus or ligaments (post-traumatic arthritis), surgery, obesity, concomitant rheumatoid arthritis, gout, diabetes, or congenital joint abnormalities [38].

There are two diagnostic definitions for OA, the first being radiographic osteoarthritis. The diagnosis of radiographic OA is made with the application of the Kellgren Lawrence classification which is a graded assessment of weight bearing films for the radiographic features of OA including joint space narrowing, subchondral sclerosis, and deformity of bone contour[38,44]. A Kellgren Lawrence grade of ≥ 2 is diagnostic of radiographic OA. The second diagnostic definition is symptomatic OA, which is the presence of radiographic OA (Kellgren Lawrence grade of ≥ 2) as well as symptoms such as pain and stiffness in the same knee [45,46]. It is important to distinguish the two because

symptomatic OA is the more clinically relevant diagnosis as it carries the most morbidity, disability, and public health burden [45]. In the Johnston County Osteoarthritis Project, it was found that though a positive association between the presence of radiographic features of OA and patients having pain exists, a large group of patients demonstrated radiographic findings that were asymptomatic and not limiting activity ([47]. The Framingham study demonstrated the prevalence of radiographic OA of the knee to be 33% (43% women, 31% men) in patients aged 63-94. In this same group, the prevalence of symptomatic OA of the knee was only 9.5% (11.4% women, 6.8% men) [36]. The incidence of OA varies due to study population age and disease definition utilized [48]. Studies that utilize radiographic diagnostic criteria result in a higher incidence rate as the severity of radiographic features and disability aren't strongly correlated [47–50].

Several risk factors for OA have been identified and include age, female gender, family history, obesity, nutrition, previous major or repeated minor trauma or surgery, occupational (athletes, laborers), joint malalignment, muscle weakness and sedentary lifestyle[275145]. In a large population-based study, the lifetime risk of developing symptomatic knee OA was found to be 44.7% (95% confidence interval [95%CI] 40.0-49.3%)[45]. When participants had a history of previous knee trauma or BMI >30, the lifetime risk rose to 56% (95% CI, 48.4-65.2) and 60.5% (95%CI, 53.0-58.1) respectively, providing proof that these risk factors are particularly important in the development of knee OA[45].

3.3 Treatment Options:

3.3.1 Non-operative treatment:

Osteoarthritis of the knee can be managed with a variety of conservative and pharmacologic options before considering surgery. Typically, these modalities are more effective with relieving symptoms in patients who have mild to moderate OA, though they should still be considered first-line therapy in all patients regardless of age, functional ability, radiographic findings, pain level, and comorbidities [52]. Conservative management includes the use of exercise, weight loss, knee braces, walking aids, transcutaneous electrical nerve stimulation (TENS), local heat, and activity modification.

These treatments have been shown to have significant benefit for patients, and are often successful with managing mild symptoms, avoiding the use of pharmacologic therapy[52].

In terms of pharmacologic management, options that can be utilized in patients with moderate to severe symptoms include oral and topical medications as well as intraarticular injections.[52,53]. Non-steroidal anti-inflammatories, selective cyclooxygenase-II (Cox-2) inhibitors, acetaminophen, tricyclic antidepressants, and selective serotonin and norepinephrine reuptake inhibitors (SNRI) make up the majority of oral pharmaceutical options in the management of osteoarthritis. Some oral supplements such as glucosamine and chondroitin can be used as well, but the evidence is conflicting in regard to their efficacy [52]. Opioids should not be routinely utilized as they come with a number of side effects such as constipation, nausea, sedation, dizziness, dependency, and addiction [52]. A large systematic review found only a small effect size (standardized mean difference (SMD-0.28, 95% CI, -0.35 to -0.20) of non-tramadol narcotics compared to placebo. This corresponds to a 0.7-point difference on the visual analogue scale for pain and a number needed to treat to produce one additional treatment response of 10 (95% CI, 8-14). This indicates that narcotics are not highly effective in the management of pain in OA [54].

Intraarticular injections consist of three categories; corticosteroids, hyaluronic acid, and platelet rich plasma. Their mechanism of action varies, but they all work by reducing intraarticular inflammation once administered inside the joint [53]. Vannabouathong et al.[55] performed a systematic review of 10 meta-analysis looking at pharmacologic treatments for knee osteoarthritis compared to oral placebo. What they found was, after controlling for the intraarticular injection placebo effect, high molecular weight hyaluronic acid injections (SMD-0.58, 95% CI, 0.36-0.79) provided the most precise treatment effect estimate that surpassed their threshold of clinical importance (set at 0.50 standard deviation). The treatment with the greatest point estimate of treatment effect was platelet rich plasma but was also the least precise (SMD-0.77, 95% CI, -0.29-1.83) indicating significant uncertainty in its results [55]. In cases of moderate to severe OA

where joint symptoms persist despite the compliant use of non-operative treatments, referral for surgery is indicated.

3.3.2 Arthroplasty

Surgical options for knee arthritis include distal femoral or proximal tibial osteotomies, unicompartmental knee arthroplasty, and total knee arthroplasty [56]. Total knee arthroplasty is the gold standard for patients who have severe OA symptoms and have failed all previously tried conservative and medical management strategies [56,57].

The first iteration of what would become the modern total knee implant was developed in 1970 by Peter Walker, John Insall, Chitranjan Ranawat, and Alan Ingis. Named the duocondylar knee, it was an anatomic, cemented, partial condylar component that preserved both cruciate ligaments. Later it evolved into the duopatellar knee design that is more closely related to current implants [58]. Today, primary total knee prostheses are comprised of two to four components of varying materials depending on the brand and model. They include a distal femoral component, a tibial base plate, tibial tray liner, a single tibial tray and liner combination implant, and patella resurfacing implant. The liner acts as a low-friction bearing surface for the femoral component to articulate with. These implants also adhere to two major design types; fixed-bearing and mobile-bearing. Though not definitively proven in the literature, mobile-bearing designs allow for motion to occur between the tibial tray and liner with the intention of reducing component wear, loosening, and subsequent failure by improving range of movement [59]. The procedure involves guided cutting and resection of the articular surfaces of the femur and tibia. During this process, the damaged articular cartilage is removed, while the surgeon also takes into account final component alignment in the sagittal and coronal planes [57]. Recent innovations include the use of computer navigation and patient specific jigs that intend to decrease error, improve accuracy, and assist in difficult primary cases where standard alignment tools can't be utilized [57,60]. Following preparation of the femur and tibia, trial components are used to ensure proper positioning and sizing of the prosthesis. The final components are then inserted using either a press-fit or cemented implant design to maintain the desired alignment and restore knee joint kinematics [57]. Patients who undergo total knee arthroplasty have

successful outcomes with significant improvement in pain and functional limitation experiences pre-operatively [5,57,61,62].

3.4 Arthroplasty in Canada:

The need for total knee arthroplasty in Canada is increasing each year. In the year 1999, the Canadian Joint Replacement Registry (CJRR) reported that 22,302 total knee replacements were performed [63]. By 2016, this number had risen to 67,169 procedures, a threefold increase in 17 years [40]. This trend is also being seen in the United States, where the number of total knee arthroplasty procedures is expected to rise by 673% from 450,000 in 2005 to 3.48 million in 2030 [64]. As the societal demand and resource utilization for this procedure has increased, our post-operative care has become more efficient allowing for patients to be discharged earlier. During that same time period, the mean length of stay in hospital shrank from a mean of 8.5 days in 1999 to 3 days by 2016 indicating our understanding of total knee arthroplasty and its post-operative care are evolving[40,63].

3.5 Post-operative Pain:

A common concern shared by patients undergoing total knee arthroplasty is how well their post-operative pain will be managed. Poorly managed pain following surgery is an important consideration as it can directly affect ambulation, sleep, ability to perform physiotherapy and result in prolonged discharge from hospital [65–68]. Factors that are associated with an increase in severity of post-operative pain include female gender, pain catastrophizing, pre-operative depression, younger age, high pre-operative pain level and longer duration of pain [66,69–71]. The acute pain following surgery is most severe in the early stages, specifically post-operative days one to three, making early intervention a priority [65,67]. Decreased ambulation and rehabilitation due to poorly managed pain can also contribute to complications such as deep vein thrombosis, pulmonary embolus, and pneumonia [72].

Studies have indicated that poorly managed acute post-operative pain also increases the risk of developing chronic pain following total joint arthroplasty [73,74]. Baker et al. [5] demonstrated chronic pain to be a stronger determinant of overall satisfaction, even more so than functional impairment, and thus acute pain can have effect on satisfaction following TKA [5]. Therefore, adequate analgesia is essential to ensure expedited discharge, decreased short and long term post-operative complications, and improved patient satisfaction.

3.6 Analgesic Medications:

As pain is a complex and difficult aspect of the post-operative management, healthcare professionals utilize a number of analgesic options to decrease the noxious stimuli that follow total knee arthroplasty. Nociceptive pain information travels towards the brain through afferent sensory nerves when they are stimulated peripherally, and analgesic medications work to inhibit this pathway at varying levels. Depending on their mechanism, common analgesic medications decrease the intensity of the pain sensory pathway by interacting with it at different levels [53]. Narcotic medications, or opioids, are utilized in the early and most severe stages of pain post-operatively [69,75]. They depress nociceptor neuron activity through the central activation of opioid receptors, resulting in analgesia at the surgical site[76]. Opioids have traditionally been delivered through patient-controlled analgesia, giving patients the choice of when to deliver doses through a computerized pump in an attempt to reduce total consumption, and maintain satisfaction [77]. Though effective, opioids come with host of adverse effects including nausea, vomiting, pruritus, urinary retention, constipation, confusion, sedation, and more severe complications like respiratory depression, tolerance, addiction, and death [75,78]. Halawi et al. [75] found in a population of 673 total joint arthroplasties, 8.5% of patients suffered from a complication as a result of narcotic medication, and these events accounted for 58.2% of the total complications in the study. As a result, length of stay was significantly prolonged ($p<0.001$) in patients who suffered from an adverse event related to opioids [75]. The demand to find effective alternative analgesics has been

present for some time now, with studies beginning as far back as 1985 looking at the effect of opioids on arthroplasty patients [78].

A more modern approach to analgesia for arthroplasty patients is the use of multi-modal analgesia. Multi-modal analgesia provides a more comprehensive analgesic strategy by using multiple drug classes for improved post-operative analgesia, decreased risk of major drug related complications, and an expedited discharge can be achieved without significant narcotic use [69,77,79]. Multi-modal analgesia combines systemic analgesics such as non-steroidal anti-inflammatories (NSAIDs), acetaminophen, neuropathic medications, and minimal opioid medications with neuraxial and peripheral anaesthetic techniques to ensure adequate pain management [79]. Lamplot et al. [77] performed a randomized controlled trial on patients who had undergone total knee arthroplasty. Patient-controlled hydromorphone analgesia served as the control group, where the experimental multi-modal group received intra-operative periarticular infiltration with bupivacaine, with scheduled post-operative opioids (oxycodone, tramadol) and NSAIDs (ketorolac). Total and daily narcotic consumption was found to be significantly lower in the multi-modal group ($p<0.0004$ and $p<0.007$ respectively). The multimodal group also had significantly less narcotic related side effects while in hospital ($p<0.01$) as well as following discharge ($p<0.01$). They also found a difference in VAS pain scores at rest ($p<0.0004$) and during activity ($p<0.001$) between groups favoring the multi-modal group and that they met physiotherapy milestones faster. As they had only blinded the outcomes assessors, a decision was made to end the trial early as there was unanimous agreement amongst care providers that multi-modal analgesia was superior [77].

3.7 Regional Anaesthesia:

Regional anaesthetic blocks provide a non-opioid option for post-operative analgesia following total knee arthroplasty and promote early ambulation, decrease opioid consumption, and as a result, decrease length of stay in hospital [12,80–82]. A common local anaesthetic that has shown to be a potent analgesic with a favorable safety profile is ropivacaine. Ropivacaine is an amino-amide local anaesthetic that blocks nerve fiber impulses through reversible inhibition of sodium ion channels, inhibiting afferent

nociceptive information [83]. Compared to other local anaesthetics such as bupivacaine, it is less lipid soluble, and thus has less risk of central nervous system and cardiac toxicity [84,85]. In the setting of regional anaesthesia, it can be combined with NSAIDs such as ketorolac, which inhibits prostaglandin inflammatory mediators, increasing its analgesic quality and further reducing opioid consumption [77]. Epinephrine can also be added to the cocktail to cause localized vasoconstriction, which prolongs the effect of the local anaesthetic by having less resorption [17]. Andersen et al. [86] compared two different local infiltration cocktails, the control being ropivacaine with epinephrine and the experimental being ropivacaine, epinephrine with ketorolac. They found that a significant reduction ($p<0.0001$) in morphine consumption at 0 to 48 hours post-op, as well as lower VAS pain scores at rest and during movement from 0 to 48 hours post op in the group who received ketorolac ($p=0.02$) [86].

Regional anaesthetic can be delivered using a number of different techniques described in the literature [87,88]. In the setting of total knee arthroplasty, common techniques include epidural analgesia, femoral nerve blocks, adductor canal block, and periarticular infiltration [88]. Both peripheral nerve blocks and periarticular infiltration decrease opioid consumption, but each have their own benefits and disadvantages [80–82]. Peripheral nerve blocks are an effective analgesic technique for total knee arthroplasty without the side effects associated with systemic or epidural analgesia. Some potential complications that can occur with peripheral blocks though include dense motor blockade that impairs early ambulation and increases the risk of falling, infection from an indwelling catheter, neurologic and vascular injury during the procedure, and anaesthetic toxicity [88,89]. Periarticular infiltration reduces the risk of motor blockade and neurovascular injury while providing excellent analgesia [82]. Its relative simplicity and reduced procedure time and cost compared to peripheral nerve blocks make it an attractive analgesic modality [88]. Difficulty with delivering continuous anesthetic to the surgical site is a limitation of periarticular infiltration. It relies on diffusion of anaesthetic within the tissue surrounding the knee to achieve analgesia, and there is apprehension in the surgical community with leaving indwelling catheters due to concerns for prosthetic joint infection [69]. An issue with the literature comparing regional anaesthetic methods is the vast heterogeneity that exists between studies because of variable

anaesthetic drug choices, concentrations, doses, infusion rates and assessment protocols. Generalizations on efficacy of analgesia, ambulation ability, morphine consumption, and complication rates are challenging to make, but consistencies are seen between studies.

3.8 Single versus Continuous Regional Anaesthetic:

Procedural options for regional anaesthesia include single-shot or continuous infusions of local anaesthetic through an indwelling catheter depending on the desired duration of analgesia and discharge plan [82]. The constant administration of local anaesthetic around a targeted nerve or the surgical site allows for effective analgesia. The benefit of having an indwelling catheter is the ability to administer further doses of anaesthetic to prolong the duration of analgesia [81,90–93]. Some concerns with continuous blocks and catheters though are the increased risk of infection, retained catheter components, catheter blockage or dislodgement, and anaesthetic toxicity [81,89,93,94]. Current evidence has provided little direction for a superior infusion medication, drug concentration, and infusion rate for continuous blocks and thus these choices are made by surgeon and anesthetist preference, resource availability, and experience [24,88].

3.9 Single-shot Adductor Canal and Motor-sparing Nerve Blocks:

The medial compartment of the thigh contains a triangular shaped canal called the adductor canal. The muscular borders of the adductor canal are formed by sartorius anteriorly, vastus medialis anterolaterally, and posteromedially by adductor longus and magnus [22,24]. The contents of the canal include the femoral artery and vein, descending genicular and muscular branches of the femoral artery, the saphenous nerve (femoral nerve sensory branch), and the nerve to vastus medialis prior to its insertion into the muscle [22,24]. First described by van der Wal in 1995, local anaesthetic can be delivered here under ultra-sound guidance or through nerve-stimulation to anaesthetize the

saphenous nerve and provide a largely isolated sensory block to the anterior aspect of the knee [24,95]. Adductor canal blocks have gained popularity in recent years due to their reduced risk of motor blockade causing quadriceps weakness which can result in delayed rehabilitation and discharge in comparison to femoral nerve blocks and epidural analgesia [24,87,90,96–98].

Prior to adductor canal blocks, femoral nerve blocks were a successful peripheral nerve block in TKA patients and removed risks like neuraxial haematomas that are associated with epidural infusions [87]. One of the complications associated with femoral nerve blocks is dense motor blockade due to the proximal site of anaesthetic administration [80,97–99]. As adductor canal blocks target saphenous nerve, a sensory branch of the femoral nerve, the risk of quadriceps weakness occurring has been shown to be significantly reduced while still providing excellent analgesia when compared to femoral nerve blocks [24,97–99]. Jaeger et al. [99] performed a randomized, double-blinded, and placebo controlled cross over study comparing quadriceps strength between adductor canal and femoral nerve blocks. Twelve volunteers received an active adductor canal or femoral nerve block randomized to either their right or left leg and a placebo in the contralateral side. Subjects returned for a second study day to receive the opposing active block depending on what they had first. Active peripheral blocks were performed using 30 milliliters (ml) of 0.1% ropivacaine, with isotonic saline as the placebo, under ultrasound guidance. The primary outcome measure was quadriceps strength measured via maximum voluntary isometric contraction (MVIC) in the leg that received an adductor canal block versus placebo. Secondary outcomes were the difference in quadriceps strength between adductor canal and femoral nerve blocks, difference in adductor strength, and mobilization at one and six hours following the procedure (timed up and go (TUG), 10-meter walk test and 30-second chair stand test). The investigators and subjects were blinded during the study and the study was sufficiently powered (power 80%, α=0.05, sample size=10). Baseline quadriceps MVIC measurements were taken, and a 25% reduction set as the minimally clinically important difference as a 10% difference between subject's legs is normal. Eleven study subject's data were analyzed finding a significant difference in MVIC between adductor canal and femoral nerve

blocks (p=0.002) as well as between placebo and femoral nerve blocks (p=0.0004). The mean difference in MVIC in adductor canal blocks was 8% less than baseline, whereas in the femoral nerve block group it was 49% less. Adductor strength was significantly different (p=0.007) between femoral nerve blocks and placebo, with femoral block causing more adduction weakness, but no difference was observed between adductor canal and femoral blocks. Regarding the functional tests, subjects demonstrated a significant reduction in time to perform both the TUG (p=0.002 at one hour, and p=0.008 at 6 hours) and 10-m walk tests (p=0.005 at one hour, and p=0.002 at 6 hours) at both assessment points with the adductor canal block compared to femoral nerve block. Additionally, adductor canal blocks offered a significant advantage over femoral nerve blocks in the 30-second chair stand test (p=0.007 at one hour, and p=0.02 at 6 hours). The most striking finding in this study was the reduction in quadriceps strength between adductor canal and femoral nerve blocks. An 8% reduction wasn't considered significant for the adductor canal block as a 10% difference can exist between subject's legs normally, but a 49% reduction from a femoral block could delay rehabilitation and increase fall risk [99].

These results have been replicated in a number of other randomized controlled trials comparing adductor canal and femoral nerve blocks [97,98]. Kwofie et al. [98] also performed a blinded randomized control trial comparing quadriceps strength between adductor canal and femoral nerve blocks. Similarly, their primary outcome was maximum voluntary contraction at 30 and 60 minutes following the procedure. Secondary outcomes included adduction strength at 30 and 60 minutes as well as Berg Balance Scale (BBS) serving as a functional outcome at 30 minutes after the block. The study protocol called for participants to receive an adductor canal block in one leg and a femoral block on the contralateral side with each block utilizing 15ml of 3% chloroprocaine under ultrasound guidance. The study was sufficiently powered with sixteen healthy volunteers (power=0.8, α= 0.05, sample size=14) enrolled and a 50% difference in quadriceps strength being set as clinically important. MVIC was significantly improved with adductor canal blocks, with a mean of 95.1% of MVIC preserved compared to only 11.1% in femoral blocks at 30 minutes following the

procedure. At 60 minutes, a significant difference was still present, with 98.8% of baseline MVIC preserved in with adductor canal blocks and 41.2% in femoral blocks. No differences in adduction strength were observed. BBS was significantly impaired in the femoral nerve block group (p=0.02) [98].

Grevstad et al.[97] reported similar findings in their 2015 study, where the difference in MVIC between adductor canal and femoral nerve blocks was compared in post-operative patients. Fifty patients were randomized to either adductor canal (n=25) or femoral nerve block (n=25) on post-operative day one or two. Patients received both procedures and blinding of the care providers was done by having pre-prepared containers containing either 30mL of 0.2% ropivacaine or 30mL of saline equally distributed between the two blocks. MVIC at 2 hours following the procedure served as the primary outcome and was expressed as a percent of the baseline MVIC. The secondary outcomes were VAS pain at rest and activity, adductor strength and the TUG test for functional assessment at 2 hours post-procedure. The minimal clinically important difference of MVIC between groups was set at 20%, and the study was sufficiently powered (power=0.9, α=0.05, sample size=22). Median MVIC significantly improved from baseline by 193% (95% CI, 143-288%) following adductor canal block versus 16% (95% CI, 3-33%) for femoral blocks, an estimated difference of 178% (95% CI, 136-226%, p<0.0001). The TUG test was performed significantly faster in the adductor canal block group with a mean difference between groups of 20 seconds (95% CI, 9-30s, p=0.001). It was also noted that six of the femoral nerve block patients were unable to perform the TUG at 2 hours due to dense motor block of the quadriceps. No differences were found in VAS scores at rest and with activity as well as adductor strength [97]. These studies unfortunately had small sample sizes and failed to compare the more clinically relevant outcomes of post-operative pain reduction and function at 24-48 hours post-op. What they did demonstrate though was the motor protecting quality of an adductor block compared to femoral nerve blocks in healthy and post-operative subjects.

Studies have shown the analgesic efficacy of adductor canal blocks and femoral nerve blocks to be similar. Kuang et al.[100] performed a systematic review and meta-analysis of

9 recent randomized controlled trials involving 609 patients (668 knees) comparing adductor canal and femoral nerve blocks with VAS scores with rest and activity as the primary outcome. Secondary outcomes included quadriceps strength (manual muscle testing (MMT) and MVIC), opioid consumption, patient satisfaction, and length of stay in hospital. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process was utilized to assess the quality of the evidence for each outcome. No significant differences in VAS scores were found at rest at 24 hours (7 studies included, p=0.97) and at 48 hours (6 studies included, p=0.23). With activity, no significant differences were found between groups at 24 hours (7 studies included, p=0.30) and 48 hours (7 studies included, p=0.18). Quadriceps strength between groups was significantly different, favoring the adductor canal block group at 24 hours (p=0.002) with MVIC, and at 8 (p=0.04), 24 (p=0.03) and 48 hours (p=0.04) with MMT. No other secondary outcomes were found to be significant between groups [100]. They concluded that adductor canal blocks can provide similar analgesia to femoral blocks, while avoiding mobility issues due to quadriceps weakness, and recommended its use in the total knee arthroplasty population.

The knee joint is innervated by the femoral and obturator nerves anterolaterally and sciatic nerve posteriorly. A motor-sparing nerve block (MSNB) includes an additional two single-shot injections in the posterior pericapsular area and around the lateral cutaneous nerve of the thigh to provide more anaesthetic coverage than a standard adductor canal block [12]. Our centre previously performed a randomized controlled trial comparing motor sparing nerve block and periarticular infiltration. Sogbein et al. [12] randomized 82 primary TKA patients to receive either a motor- sparing nerve block (experimental, n = 41) or periarticular infiltration (control, n = 41) to compare between-group duration of analgesia. Patients were enrolled between July 2014 and June 2015 and randomization was stratified by age and surgeon to ensure that the groups were balanced with respect to these factors. The primary outcome measurement was analgesic duration, measured as time from end of MSNB/Infiltration administration to end of effective analgesia (i.e. pain score at rest/activity >6 on the 11-point NRS and initiation of rescue analgesia). Secondary outcomes included quadriceps strength (MVIC), TUG test, patient reported outcome data (Western Ontario and McMaster

University Osteoarthritis Index, Short-Form-12 Survey, and Knee Society Score), narcotic consumption and side effects, and length of stay. Both the motor-sparing nerve block and infiltration groups received a drug cocktail of 0.5% ropivacaine, 2.5mcg/mL epinephrine, 10mg of morphine, and 30mg of ketorolac. The motor-sparing nerve block consisted of a posterior knee infiltration injection of 20mL, a lateral cutaneous nerve of the thigh block with 5mL, an intermediate cutaneous nerve of the thigh block delivered under the fascia lata at mid-thigh of 10mL and finally, the adductor canal was injected with 25mL for a total of 60mL**.** Intraoperatively, the periarticular infiltration group was infiltrated with 100mL of the study drug. Randomization was performed by research assistants not involved in the study, while the patients, surgeons, anaesthetists, and outcome assessors were all blinded to avoid selection, performance, and detection biases. Patients were analyzed on an intention-to- treat basis, using ANCOVA to compare outcomes and a post-hoc Bonferroni correction to adjust for multiple comparisons error. The study was sufficiently powered and used an equality sample-size calculation to detect the minimal clinically important difference (power=0.8, α=0.05). MSNB provided significantly longer duration of analgesic effect, with a mean difference of 8.8 hours (95% CI= 3.98-13.62 hours, p<0.01) compared to periarticular infiltration. MSNB also had statistically significant lower pain scores at 2- and 4-hours post-op with activity, and 2 hours post-op at rest. All other time points and secondary outcomes did not show significant differences. The results provided evidence that MSNB is a suitable technique for pain management following TKA [12]. This study was considered part-one of a two-part regional anaesthetic trial and the methodology and results framed what would become the current study.

3.10 Local Wound Infiltration:

In 2008, Kerr and Kohan first described in a non-randomized case series a multi-modal anaesthetic technique they coined local infiltration analgesia (LIA), also known as periarticular infiltration [101]. Though wound infiltration with anaesthetic was not a new concept, the use of large volumes combined with specific injection placement hadn't

been described in the literature previously. The tissues surrounding the knee including the posterior joint capsule (30-50mL), lateral and medial joint tissue (30-50mL) as well as the anterior wound edges (25-50mL) were systematically infiltrated with a total of 150-170mL of the study drug (0.2% ropivacaine, 10mcg/mL epinephrine, and 30mg ketorolac) to provide complete anaesthetic coverage. An intra-articular catheter was placed for bolus injections at the end of the surgical case. Their results were positive, with 71% of patients being discharged post-op day 1 and no serious adverse effects noted throughout the trial period [101]. Similar to peripheral nerve blocks, LIA has demonstrated a number of benefits over previous analgesic techniques. LIA has been shown to decrease post-operative pain scores, decrease narcotic consumption, improve early function and ambulation, and have less risk of complications associated with some other regional anaesthetic procedures [17,77,81,82,88,101,102].

Busch et al. [17] performed a randomized controlled trial of 64 TKA patients comparing LIA (n=32) to no injection (n=32). Patients were blinded as to what group they were randomized to and the experimental injection consisted of a 100mL mixture of 400mg ropivacaine, 30mg ketorolac, 5mg of epimorphine, and 0.6mL of epinephrine. Narcotic consumption in the first 24 hours served as the primary outcome, with secondary outcomes including VAS scores for pain and satisfaction, patient reported outcomes (WOMAC, KSS), length of stay, and complications. Five patients had serum ropivacaine levels drawn at 30 minutes, 1 hour, and 4 hours post-op and all patients underwent a post-operative lower limb ultrasound for deep vein thrombosis (DVT) at post-op day 5. In the infiltration group, narcotic consumption through PCA was significantly less at 6 hours ($p<0.01$),12 hours ($p=0.016$), and overall at 24 hours post-op ($p<0.001$). VAS pain scores were significantly less in the post-anaesthetic care unit (PACU) ($p=0.04$) as well as 4 hours post-op ($p=0.007$). Satisfaction scores were significantly higher in the LIA group in PACU ($p=0.016$) and four hours post-op ($p=0.016$). None of the experimental patients demonstrated toxic levels of serum ropivacaine, with the highest level being 2.5 times less than the level of toxicity, and one patient suffered a DVT in the infiltration group. No other significant differences were present between groups. In conclusion, they recommended the use of LIA in patients undergoing total knee arthroplasty as it decreased narcotic consumption and improved pain scores and satisfaction [17]. The

results of this study were supported in a recent systematic review and meta-analysis of 38 RCTs by Seangleuluret al. [103] where LIA had significantly decreased VAS rest pain scores at 24 hours post-op versus placebo or no injection after sensitivity analysis was performed to remove narcotic and NSAIDs as potential confounders (n=24 studies). Narcotic consumption at 24 (n=20 studies) and 48 hours (n= 10 studies) was also significantly reduced in the LIA group compared to placebo or no injection. LIA patients also had a shorter length of stay in hospital compared to controls (n=9 studies) [103].

Similar to adductor canal blocks, periarticular infiltration shares the benefit of sparing motor function to the quadriceps muscles, resulting in less risk of weakness and delayed rehabilitation. Li et al. [104] randomized 82 patients into three different groups, LIA (n=26), adductor canal block (n=26), and femoral nerve block (n=29) to compare numerical rating score (NRS) pain scores at rest and activity at 2, 6, 12, 24, 36, 48, and 72 hours post-op. Secondary outcomes included quadriceps and adductor strength at the same time intervals using MMT, knee range of movement, TUG test, as well as total daily ambulation. The peripheral nerve blocks were performed under ultrasound with 20mL 5g/L ropivacaine and 0.1mg adrenaline, and periarticular infiltration was with 90mL total of 2.5g/L ropivacaine and 0.1mg adrenaline injected throughout the joint. Final analysis included 77 patients and revealed that LIA had significant lower NRS scores than the nerve block groups at rest at 2, 6, and 12 hours post-op ($p<0.05$). No differences were present at any other time points or during activity at any time points between groups. The LIA group had significantly less total narcotic consumption when compared to the nerve block groups ($p<0.05$). Quadriceps weakness was significantly increased in the femoral nerve block group within the first 12 hours, but not after ($p<0.05$). A significant difference in TUG test and daily ambulation distance was also present, favoring LIA on post-op day one over both nerve block groups ($p<0.05$), and was only significantly different from femoral nerve blocks on post-op day two ($p<0.05$). The length of stay for the LIA group was significant as well, demonstrating a shorter inpatient period compared to the nerve block groups ($p<0.05$) [104]. This was a small study, with little information being provided in regard to their power calculation, and it likely was underpowered to make any definitive conclusions.

A recent meta-analysis of 14 trials, including 1122 patients comparing LIA with femoral nerve blocks contradicted these results, finding no statistically significant differences between groups regarding narcotic consumption, pain scores at rest and activity, functional outcomes and complications. They warned readers though to interpret the results with caution as significant heterogeneity between studies existed and no firm conclusions could be made [20].

Sardana et al. [105] reviewed the literature and compared LIA analgesia with adductor canal blocks following total knee arthroplasty. They conducted a meta-analysis including 6 studies of 396 patients that had a high amount of agreement among quality assessment scores using the Jadad scale. Quantitative analysis revealed the VAS pain scores for the LIA group were significantly reduced ($p=0.001$) compared to adductor canal blocks. A similar result was found when comparing the narcotic consumption, with LIA have significantly less ($p=0.03$). Unfortunately, functional outcomes were not able to be analyzed due to the significant heterogeneity between studies. They concluded that LIA has the potential to improve post-operative pain and reduce narcotic consumption compared to adductor canal blocks but could not make any definitive conclusions, stating more literature is needed [105].

One of the limitations of LIA is the short duration of effective analgesia, ranging from 8-48 hours, and the challenge of developing a reliable method of continuous deliver anaesthetic post-operatively [81,105]. Numerous studies have been performed exploring the idea using different medications, drug concentrations, and infusion rates with variable results [106–110]

3.11 Continuous Epidurals Analgesia:

Continuous epidural analgesia involves the placement of am indwelling catheter into the epidural space to prolong the analgesic effect similar to peripheral nerve blocks. Prior to the wide spread use of peripheral nerve blocks, neuraxial anaesthesia was a successful regional analgesic option in orthopaedic surgery. Epidural analgesia has fallen out of

favor though due to its tendency to cause concomitant motor block and concerns over its safety profile [111,112]. Neuraxial haematoma is a risk following epidural and is increased in orthopaedic patients (1:4000) compared to other surgical procedures (1:10000-20000). The reason for this is the use of early anti-coagulation in this patient population due to the increased risk of venous thromboembolism [87,111]. Gerrard et al. [96] performed a meta-analysis of 12 randomized trials comparing peripheral nerve blocks to epidural analgesia and found that there were no statistically significant differences in VAS pain scores a 0-12, 12-24, and 24-48 hours post-op between the two groups. What was found was that epidurals significantly increased the risk of post-operative complications including nausea and vomiting ($p=0.002$), hypotension ($p=0.0009$), and urinary retention ($p<0.0001$) [96]. Peripheral nerve blocks provide the same analgesic benefit of epidural analgesia with less risk of complications [112].

3.12 Continuous femoral nerve blocks:

Femoral nerve blocks are a common regional anaesthetic technique due to their low procedural difficulty and success with lower limb analgesia [113]. First described by Labat in 1920, they have risen in popularity in the last few decades in the orthopaedic community [113–115]. Local anaesthetic can be delivered through a single-shot or through a perineural catheter to prolong the analgesic effect [80,113].

Chan et.al.[113] randomized 200 patients prior to undergoing total knee arthroplasty to three treatment options, Intravenous PCA (1mg morphine, 10mg/hr lockout), single-injection femoral nerve block (20mL 0.25% bupivacaine with 2.5mcg/mL adrenaline), and continuous femoral nerve block (20mL 0.25% bupivacaine with 2.5mcg/mL adrenaline injection, followed by 0.125% bupivacaine 4mL/hr infusion). The primary outcome for the study was significant pain with activity, defined as a VAS pain score of greater than 4. Secondary outcomes included VAS pain score at rest, cumulative narcotic consumption, side effects such as nausea and vomiting, number of days to achieve 90 degrees of flexion range of motion, and complications. The study was sufficiently powered, with a sample size of 60 (power=0.8, α=0.05) being calculated for

the primary outcome. At the time of analysis, 64 patients were in the PCA group, 68 in the single-injection group and 65 in the continuous infusion. Compared to PCA, the proportion of patients who suffered from significant pain (VAS>4) was found to be significantly lower in both the single-injection femoral block (OR 0.36; 95% CI 0.15 – 0.86; p=0.022) and continuous groups (OR 0.25; 95% CI 0.11 – 0.6; p=0.002). VAS pain scores at rest were significantly lower in the continuous femoral block at 6 hours post-op compared to PCA (p=0.018). VAS pain score with activity was found to be significantly lower in both the single-injection group (p=0.045) and continuous femoral nerve block group (p<0.0001) compared to PCA at 24 hours post-op. A significant difference was also found at 24 hours between the two peripheral block interventions, favoring the continuous nerve block (p=0.045), indicating the duration of effective analgesia for the single-injection had passed. Both groups had significantly lower cumulative narcotic consumption compared to PCA, and continuous peripheral nerve blocks had significantly lower consumption than single-injection on post-op day 1 (p<0.001) and 2 (p<0.001). Regarding time to reach 90 degrees of flexion, both single-injection (2.3 days, p=0.014) and continuous nerve block (2.4 days, p=0.024) groups reached it significantly earlier than PCA (3 days). Nausea and vomiting were significantly less evident in the nerve block groups, and no adverse events occurred during the study period. They concluded that femoral nerve blocks provided superior analgesia over PCA, with possible additional benefits of decreased narcotic consumption, earlier functional recovery, and less side effects. Unfortunately, there was no blinding at any level (patient, provide, or outcome assessor) during the study and they recognized that small treatment benefit differences between single and continuous femoral nerve blocks could not be found as their study wasn't sufficiently powered to do so [113].

Certain complications are a major concern with femoral nerve blocks. Feibel et al. [13] performed a retrospective review of patients who underwent total knee arthroplasty and received a femoral nerve perineural catheter. Two groups of patients were established, a group of 469 patients who had a femoral block infusion for 2-3 days post-op and another 721 patients whose infusion was discontinued 12 hours post-op. In the 469-patient group, 0.4% (n=2) suffered a nerve palsy, and 0.85% (n=4) sustained a fall due

to motor weakness while in the 721-patient group, nerve palsies occurred in 1% (n=7), with 0.2% (n=2) being permanent, and 0.55% (n=4) of patients had a fall. The overall incidence of neurologic injury was found to be 0.6% in this study but has been quoted to be as high as 1.2% following TKA [13,116]. Though rare, neurologic injury possess a potentially catastrophic outcome in TKA patients and patients should be cautioned. Transient motor weakness is also an issue with femoral nerve blocks [89,90,93,113]. The rectus femoris, a major contributor to active knee extension, receives motor function from two nerve branches of the femoral nerve. An anatomical study with cadaveric specimens found the proximal and distal motor branches to rectus femoris can be found 8±2.12cm and 17.25±5.21cm distal to the femoral nerve at the inguinal ligament respectively [117]. The insertion site for the femoral block is proximal to both of these motor branches and thus explains why quadriceps motor function can be compromised following a femoral block [80,97–99]. As a result of this, along with the success of adductor blocks and Infiltration for analgesia, femoral nerve blocks have become a less attractive option in modern arthroplasty care [114].

3.13 Continuous adductor canal blocks:

Similar to femoral nerve blocks, adductor canal blocks offer the option of adding a perineural catheter to extend the duration of analgesia past what single-injection techniques can provide [80]. The benefit of adductor canal blocks compared to femoral nerve blocks and epidural analgesia is the decreased risk of quadriceps weakness which can limit rehabilitation and delay discharge [80,118,119].

Shah et al. [91] performed a randomized control trial comparing single-injection versus continuous adductor canal blocks. The sample included 46 continuous and 39 single-injection participants and was sufficiently powered to detect a clinically significant difference of 10mm in VAS score (power=0.8, α=0.05, sample size=44). The single-injection consisted of 30cc 0.75% ropivacaine injection, followed by repeated 30cc saline boluses every 4 hours post-op. The continuous adductor canal block group received a 30cc 0.75% ropivacaine injection as well, but a 30cc 0.25% ropivacaine

bolus was delivered every 4 hours post-op. The primary outcome was VAS pain score at 4, 8, 12, and 24 hours post-op, with secondary outcomes including TUG test, 10-m walk test, 30s chair test, ambulation distance at discharge, maximum knee flexion at discharge, and length of stay. They found that the continuous group had statistically significant lower VAS pain scores at rest and during activity at 4, 8 ,12, and 24 hours post op ($p<0.001$). There was also a significant difference in pain scores favoring the continuous block group at rest and activity on post-op day 1 and 2 ($p<0.001$, $p<0.001$). The timed up and go, 10-m walk, and 30s chair tests were used to assess ambulation ability and though the continuous group had faster times, they were not significant. Functional recovery outcomes (staircase competency, walker ambulation, ambulation distance, flexion range at discharge) demonstrated no significant differences. Two patients in the single-injection group required rescue opioid analgesia and none in the continuous group, which was consistent with other studies. No other secondary outcomes were found to have significant differences. They concluded at the end of this study that adductor canal blocks provide excellent analgesia following TKA, with continuous adductor canal blocks demonstrating superior analgesia over single-injection [91].

One would expect this outcome, as intuitively, having the ability to deliver more anaesthetic over time should yield a longer duration of analgesia. However, the results comparing single-shot and continuous adductor canal blocks have been inconsistent. Zhang et al. [120] performed a randomized, placebo-controlled trial comparing single-shot adductor canal block, continuous adductor canal block and a saline control group (Y zhang, ultrasound). The single-injection consisted of an ultrasound guided 20mL 0.5% ropivacaine pre-operatively followed by two 20mL saline boluses at 12- and 24-hours post-op. The continuous group received the same pre-operative regimen, with 20mLof 0.5% ropivacaine given at 12 and 24 hours, and the saline control group received saline for all three injections. The primary outcome was visual analogue scale for pain during activity, with secondary outcomes including opioid consumption, quadriceps strength, range of motion, procedural time and complications. The results showed no differences in any outcome measures except procedural time (single-injection; 4 ± 1.4 minutes versus continuous; 20 ± 5.0 minutes) when comparing the single injection and

continuous adductor blocks. The continuous group had a vascular injury at the time of catheter insertion and one catheter accidentally dislodged from its insertion site. Considering the similar outcome measures, extra time involved to place the catheter, catheter cost, as well as increased risk of complications in the continuous group, they recommended using a single-injection technique for adductor canal blockade [120]. Some studies have yielded similar results to support these findings. Turner et al. [121] found that single-injection adductor canal blocks with multiple adjuvants (clonidine, dexamethasone and epinephrine) provided analgesia that was equivalent to a continuous adductor canal block up to 36 hours, though at 42 hours and beyond the continuous group was more effective [121]. Lee et al. [122] performed a randomized non-inferiority study comparing the single injection and continuous adductor canal block's narcotic consumption at 12,24, and 48 hours post op, and failed to demonstrate that single-injection adductor blocks were inferior to continuous blocks for narcotic consumption at 12- and 24-hours post-op [122].

Mudumbai et al. [119] sought to compare continuous adductor canal blocks with continuous femoral nerve blocks. The primary outcome was total ambulation distance achieved on post-op day 1 and 2. They set the minimal clinically important difference in ambulation distance at twice the distance in the adductor canal group compared to the femoral nerve block group. The study was sufficiently powered (power=0.8, α= 0.05, sample size=88) with 102 patients receiving a femoral nerve block and 66 receiving an adductor canal block. Secondary measures included daily narcotic consumption, pain scores and length of stay in hospital. The results for the primary outcome showed that the adductor canal block group (37m, range 0–90m) had greater ambulation distance than the femoral group (6m, range 0–51m) on (p=0.001). These results carried forward to post-op day 2, with adductor canal blocks (60m, range 0-120) being superior to femoral blocks (21m, 0-78m) (p=0.003). These results were confirmed with the use an adjusted linear regression model. No differences in any other outcome measures were found. This study demonstrated the significant motor sparing benefits involved with adductor canal blocks over femoral nerve blocks [119].

In 2018, Leung et al. [123] conducted a randomized controlled trial comparing continuous adductor canal blocks with a control group. After exclusion and patient drop-outs, 70 patients were included in the study, with 31 patients in the control and 39 patients in the continuous adductor canal group. They set their primary outcome as total opioid consumption in morphine equivalents. Secondary outcome measures were VAS pain scores measured as the area under the curve in the first 12- and 20-hours post-op, inpatient length of stay, knee range of motion, ambulation distance, and WOMAC scores. Blinding of the patients, as well as the outcome assessor was performed. The study was sufficiently powered, after setting a reduction of 20mg in opioid consumption to be clinically significant. The adductor canal block was performed under ultrasound guidance, with a bolus of 10ml of 0.25% bupivacaine into the adductor canal, followed by an 8ml/hr 0.125% bupivacaine infusion. The control group received a shame catheter through a simulated procedure, without perforation of the skin with a catheter to protect patients from unneeded harm. The study results revealed a significant increase in opioid consumption within the control group compared to the adductor canal block group at 20 hours post-op (96.5 ± 47 mg vs. 73.9 ± 38 mg, 95% CI: −43.1 to −1.94 mg, p=0.03), but not at 12 hours (11.9 ± 14 mg vs. 12.5 ± 15 mg, 95% CI: −6.6–7.6 mg, p=0.89). No difference was found VAS pain scores between the two groups at 12 hours post-op (p=0.82) but were significantly improved at 20 hours post-op for the experimental group (adductor canal block) (p=0.04). No significant difference in length of stay was observed, and WOMAC scores at 6 weeks were present. With paired outcomes at 3- and 6-weeks post-op for range of motion, there was a significant improvement in range of motion compared to baseline range within the continuous adductor canal group (p=0.01). This study provided recent evidence for the efficacy of adductor canal blocks following total knee arthroplasty [123].

Though the results with adductor canal blocks have been largely positive, there are still several factors that inhibit their wide-spread implementation. Nerve blocks are carried out prior to surgery and require resources such as regional block specialists, dedicated space, and ultrasound that add to the overall treatment cost. They also come with a host of risks, with procedure specific complications including neurovascular injury, dense motor blockade, and catheter site complications.

3.14 Continuous Wound Infusions:

There has been a wide variety of techniques described for directly delivering anaesthetic to the knee joint including single-dose intraarticular injection, periarticular infiltration where multiple sites are systematically injected around the joint prior to wound closure, intraoperative placement of an Indwelling catheter with post-operative intermittent bolus or continuous infusion, or a combination of these methods [82,124]. The use of indwelling catheters for wound infusion is similar to continuous perineural catheters in that the goal of treatment is to extend the duration of effective analgesia [81]. Though there is concern in the surgical community though that indwelling catheters surrounding a prosthesis increases the risk of infection, studies that have explored the idea of continuous periarticular techniques have yielded variable results in terms of the risk of infection as well as its analgesic efficacy [81,106,110,125,126]

Ali et al. [110] conducted a randomized control trial comparing intraarticular catheters to single-injection periarticular infiltration in 200 patients undergoing total knee arthroplasty. In the experimental group (n=100), ropivacaine was infused intraarticularly, while saline was used in the control group (n=100). Intra-operatively, both groups received periarticular infiltration with 106mL of 2mg/ml ropivacaine, 30mg ketorolac and 0.5mg epinephrine, and thus the comparison between a single injection and continuous method was made though this was not specifically stated. The continuous group's infusion consisted of 7.5mg/ml ropivacaine set a t a rate of 2mL/hr, while the control received saline at the same rate. Their primary outcome measure was VAS score for pain, with secondary measures being complications, length of stay in hospital, opioid consumption, nausea and vomiting, range of movement and ability to straight leg raise. Continuous intraarticular infusion was found to only provide a statistically significant decrease in pain scores on post-op day one (12pm; p=0.02, 8pm p=0.03). None of the other time points on post-op day two or three were significant, and secondary outcomes were also insignificant. Infection was a clinically significant complication and occurred in 13 patients in the study, 11 being in the experimental group (6 superficial, 5 deep infections) and 2 in the control (1 superficial, and 1 deep). All deep infections required surgery for their management (4 irrigation and debridement with polyethylene

exchange, two 2-stage revisions). Thus, continuous infusion did not extend the duration of analgesia as significantly as they had hypothesized and carried an increased risk of infection [110].

Sun et al. [81] performed a meta-analysis of 10 clinical trials utilizing intra-articular infusion catheters versus placebo in 735 patients. Outcomes that were assessed were VAS scores a rest and activity at 24, 48, and 72 hours post-op, duration of surgery, length of stay in hospital, and complications. Their results revealed that continuous intra-articular infusion provided statistically significant decrease in VAS pain scores at 24 hours during rest (n=8 studies, $p<0.01$) and activity (n= 5 studies, $p<0.01$) and with activity at 48 hours (n=5 studies, $p<0.01$). Continuous wound infusion was also associated with a significant decrease in nausea and vomiting ($p=0.03$). There were no differences in regard to pain at rest at 48 hours as well as during rest and activity at 72 hours between groups and length of stay was found not to be significantly different. What was significant between groups was the rate of infection, with the continuous infusion demonstrating an increased risk (RR 3.61; CI 95%, 1.18-8.5, $p=0.02$). Other complications such as DVT were not significantly different between groups. Sun et al. concluded that there was significant heterogeneity between studies due to the differences in study protocol and that there was a small number of trials (n=10) included with small sample sizes. Their results suggested that though continuous infusion provides prolonged analgesia at 24 hours with rest and mobilization and at 48 hours with mobilization, caution should be taken with its use until higher quality studies can definitively determine the risks such as infection [81].

Randomized controlled trials directly comparing single-dose periarticular infiltration to continuous intraarticular are limited within the literature. Zhang et al. [125] randomized 96 patients (80 completed the trial) to three different treatment groups, single-dose periarticular infiltration (n=27), continuous intra-articular infusion (n=27), and saline control group (n=26). The goal of the study was to provide evidence that continuous wound infusion would provide a longer duration of analgesia compared to a single-dose periarticular infiltration. The protocol called for periarticular infiltration of 150mL of 2mg/mL ropivacaine, 30mg ketorolac and 0.5mg adrenaline in both the single and

continuous groups. Following surgery, the continuous group received a 4mL/hr infusion of 2mg/mL ropivacaine, and a 1.25mg/hr infusion of ketorolac for 48 hours. The primary outcome was VAS pain scores at 2, 4, 8, 12, 16, 20, 24, 30, 36, and 48 hours, with morphine consumption, functional recovery (maximum knee flexion at 7- and 90-days post-op), patient satisfaction and complications all serving as secondary outcomes. The analysis revealed that VAS scores were lower in the continuous infusion group compared to the single-dose infiltration group and were statistically significant at rest ($p<0.05$) from 8 to 48 hours post-op and during activity ($p<0.05$) from 16 to 48 hours post-op. Morphine consumption was significantly higher in the single-dose infiltration group ($p<0.05$). Maximum knee flexion at 7-and 90-days post-op was significantly increased in the continuous infusion group as well ($p<0.05$). The incidence of nausea and vomiting was higher in the saline control group compared to the peripheral block groups but was not statistically significant. Complications, infection, and satisfaction were not statistically significant between the single-injection and continuous groups. The results of this study indicated that, as hypothesized, continuous intraarticular infusion resulted in longer duration and superior analgesia over single- injection without a significant increase in complications [106].

3.15 Summary:

Pain following total knee arthroplasty is a complex issue. Patients have variable responses and anticipating their pain level can be challenging. Inadequate management of pain following surgery can lead to delays in mobilization, discharge, and an increased risk of complications such as deep vein thrombosis, pulmonary emboli, and pneumonia. Multi-modal analgesia utilizing oral medications and regional anaesthesia is an effective and safe method to manage patient's pain following TKA, while reducing narcotic consumption and associated adverse effects [79]. Regional nerve blocks provide a variety of benefits that include decreased opioid consumption, increased mobilization, increased patient satisfaction, and decreased post-operative complications by promoting ambulation [80]. While single-injection techniques for these nerve blocks are effective, their duration of analgesia does not span the early phase post-operatively

when pain is at its worst [80,81]. Continuous MSNB provides patients with effective analgesia over a longer duration compared to single-injection techniques and improved quadriceps function over femoral nerve blocks and epidural analgesia. This makes the use of continuous regional methods more appealing, but unfortunately, they are not a feasible option for all centers that perform total knee arthroplasty due to cost and resource constraints. Novel techniques for continuous regional anaesthesia need to be cost-effective, encourage narcotic stewardship, promote early ambulation to expedite discharge, and be void of complications such as increased infection, dense motor blockade, or high rate of failure. Periarticular infiltration and infusion may fulfill these criteria. Therefore, a randomized control trial comparing its efficacy to that of MSNB would add valuable information to the literature and perhaps a feasible option for surgeons who don’t have access to peripheral nerve blocks for their TKA patients.

Chapter 4

4 Objectives

The primary purpose of this randomized controlled trial is to assess whether periarticular infiltration and infusion has a comparable time-to-discharge to that of our previously investigated motor-sparing block technique in patients who have undergone primary total knee arthroplasty. Our secondary objectives are to compare the two groups analgesic quality through visual analogue scores, narcotic consumption and side effects, and physiotherapy progress including ability to perform and range of motion during assessments. We will investigate the rate of general and specific complications associated with each of the study arms. We also will be collecting patient reported and functional outcome scores using the Western Ontario McMaster Osteoarthritis Index and Knee Society Score. Patient satisfaction and quality of life will be measured using the Short Form 12 Survey.

We hypothesize that there will be no difference in the time to discharge between our experimental group, periarticular infiltration and infusion, and our control, motor-sparing nerve block following primary total knee arthroplasty. We further hypothesize that periarticular infiltration and infusion will provide a comparable analgesic quality, physiotherapy progress, and narcotic consumption to that of motor-sparing nerve blocks while reducing procedure specific risks such as dense motor blockade. In doing this, we hope to provide evidence that supports the use of periarticular infusion so that resource constrained centers have a feasible anaesthetic option that is effective, promotes narcotic stewardship, and has minimal risk following primary total knee arthroplasty.

Chapter 5

5 Materials and Methods

5.1 Study Design:

This regional anaesthesia study was conducted between September 2017 and June 2018 (data collection ongoing) at London Health Sciences Centre (LHSC), University Hospital in London, Ontario. The study design was a non-blinded, randomized control trial with patients undergoing primary total knee arthroplasty. The study population was extracted from the practices of three staff arthroplasty surgeons following full-board ethical review and approval from the University of Western Ontario's Human Subjects Research Ethics Board.

5.2 Eligibility:

Patients were identified through the internal appointment scheduling software (App Bar), having been scheduled for a unilateral, primary total arthroplasty procedure by one of the three participating study surgeons at LHSC, University Hospital. Our inclusion and exclusion criteria are listed in table 6. An initial screening for eligibility was conducted through the available clinical documents and information provided in our center's electronic medical record. An inability to provide informed consent or perform study tasks due to psychiatric illness or cognitive impairment was set as an exclusion criterion. Patients with an allergy or intolerance to any of the pre-op, procedure related, or post-op medications were excluded. Patients who had a documented American Society of Anaesthesiologists (ASA) status of four from a previous surgical procedure, a history of chronic renal failure, had an absolute contraindication to regional and/or spinal anaesthesia, or were wheel-chair bound at the time of consultation were also excluded. A body mass index (BMI) of greater than 45 as well as long-term narcotic use/dependency or chronic pain (identified through the use of long-term use of potent analgesics) made patients ineligible for study inclusion. Potential participants who were

deemed appropriate for study involvement were approached in the preadmission clinic, where a secondary inclusion/exclusion screening took place.

Table 6: Study Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
1. Adult patients ASA physical status 1-3 2. Ability to give informed consent 3. No contraindications to regional techniques 4. Ability to perform study related tests 5. Scheduled for primary unilateral total knee arthroplasty	1. Revision arthroplasty 2. Allergy to local anesthetics and multimodal analgesic drugs 3. Contraindications to spinal anaesthesia 4. Inability to perform study related procedures 5. Inability to give informed consent 6. Wheel chair bound 7. Pregnancy 8. Chronic renal failure 9. BMI >45 10. Chronic pain managed with long-term opioid analgesia

5.3 Subject Recruitment:

Potential candidates who had received a consultation and booking for surgery by one of three participating arthroplasty surgeons were initially identified and pre-screened using our center's electronic medical record. They were then formally approached for recruitment and screened for exclusion criteria in the surgical pre-admission clinic within three months of the time of surgery. Upon recruitment, several baseline patient characteristics were collected; Age, body mass index, date of surgery, side of surgery, previous surgery on operative knee, pre-operative diagnosis, and pre-operative analgesic regimen.

5.4 Randomization:

Randomization in this study was non-centralized and was performed using a random number generation method in Microsoft excel and sealed envelope allocation technique. Permuted block randomization into sets of 10 was utilized, with a one-to-one allocation ratio, to avoid having an unequal distribution of the two possible procedures throughout the trial (e.g. a span of 15 MSNB patients at the end of the trial). A third party not involved in the assessment of outcomes performed the random number generation in excel and group allocation was placed in a sealed envelope labelled with the corresponding study number. No stratification was performed.

5.5 Blinding:

There was no blinding in this randomized control trial for cost and logistical reasons. Performing two procedures, with one being a sham, would have been cost prohibitive for the trial due to the staff, and resources needed to perform both blocks. The logistics of implementing a sham block would have required independent anaesthesiologist involvement to avoid unblinding the care givers and the outcome assessors to mix the required injections and infusions. To avoid these logistical issues the study was left unblinded.

5.6 Interventions:

5.6.1 Motor-Sparing Nerve Block Control Group:

This is a pre-operative regional anaesthetic technique that is conducted in the block room of our center's PACU by a staff anaesthesiologist. For the purpose of having the ability to compare our results to part one of this two-part RCT, we utilized the same four injection site technique[12]. This block differs to a standard adductor canal block in that there are additional anaesthetic injections covering the posterior pericapsular area and lateral femoral cutaneous nerve to provide more widespread analgesia. Prior to initial

injection, midazolam intravenously was administered at the discretion of the anaesthesiologist to allow for patient sedation. Patient vitals were monitored using an electrocardiogram (ECG), pulse oximetry, and a non-invasive blood pressure monitor. With the patient supine, positioning the operative/procedure limb involved slight flexion of knee, with external rotation at the hip and was followed by an initial pre-procedural scan assessing the four injection areas of interest. Sterile preparation of the leg was done with the use of dyed chlorohexidine and sterile draping to reduce the risk of site infection.

The initial bolus injection cocktail was prepared in the block room at the time of the procedure. With the use of a 60 mL sterile syringe, a solution containing 0.5% ropivacaine, 2.5 ug/ml of epinephrine, 10 mg of morphine, and 30 mg of ketorolac for a total volume of 60mL. The solution was injected at the four following sites, intermediate cutaneous nerve of the thigh, adductor canal (where the continuous catheter is placed), posterior pericapsular injection, and lateral femoral cutaneous nerve to provide a thorough regional block.

5.6.1.1 Intermediate Cutaneous Nerve of the Thigh (5mL bolus):

The first step of the procedure was the identification of neurovascular structures in the lower limb with the use of ultrasound guidance. The femoral artery was identified proximally at the groin and is traced along its path deep to the sartorius muscle. Once the superior geniculate artery branch is located, the probe is turned 90 degrees and moved superiorly again 8 to 10cm proximally and is marked as the site for injection. What is looked for on ultrasound is the presence of a peripheral nerve laying in the intermuscular plane between the rectus femoris and Sartorius muscles superficial to the fascia lata. Following local skin anaesthesia with 1% lidocaine injection, an eight-centimeter Tuohy block needle is inserted at the pre-marked site, avoiding the major neurovascular structures with the safe guidance of ultrasound. Once the needle is superficial to the facia lata, the tip is redirected within the fascia of sartorius and 5mL of the injection solution is delivered in the perineural area of the intermediate cutaneous nerve of the thigh (figure 7).

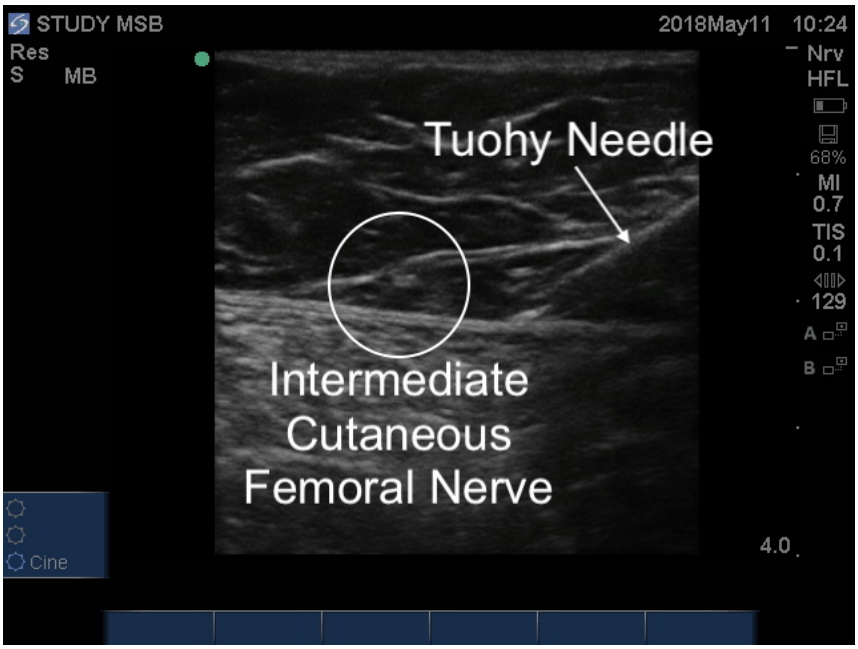


Figure 7: Ultrasound Image of the intermediate cutaneous nerve of the thigh injection

5.6.1.2 Adductor Canal (25mL bolus):

Following the intermediate cutaneous nerve of the thigh injection, the needle is simply redirected and advanced through the facia lata until the tip lies adjacent to the femoral artery, deep to sartorius. A further local anaesthetic bolus of 20ml is delivered within the adductor canal while being monitored on ultrasound using a colour doppler to ensure proper needle tip placement and study drug administration around the femoral artery and saphenous nerve. Prior to removal of the Tuohy needle, a flexible regional catheter is placed using the seldinger technique, with the tip extending 3cm past the tip of the needle. A further 5mL of study drug are delivered through the catheter for a total of 25mL of study solution being injected into the adductor canal (figure 8). The catheter insertion site is covered by a sterile tegaderm dressing and the free end of the catheter is attached to an adaptor that allows for the CADD infusion line to be connected, followed by being secured to the patient's leg or abdomen (figure 9).

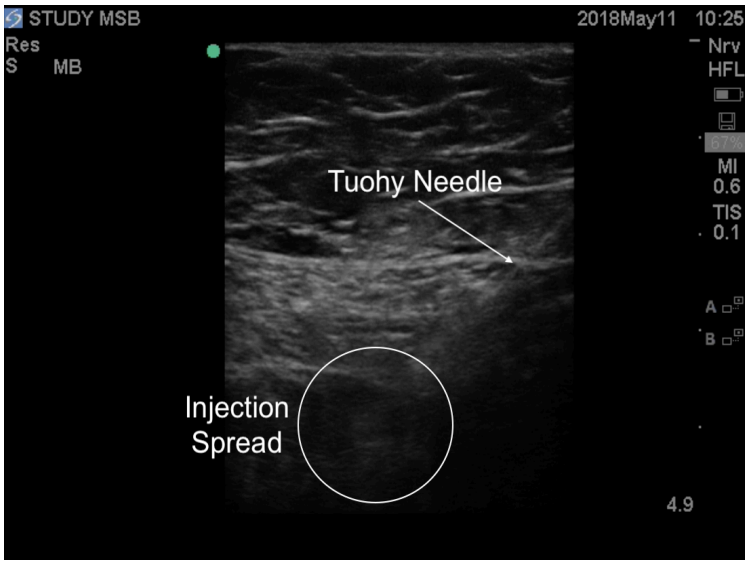


Figure 8: Ultrasound image of the adductor canal injection

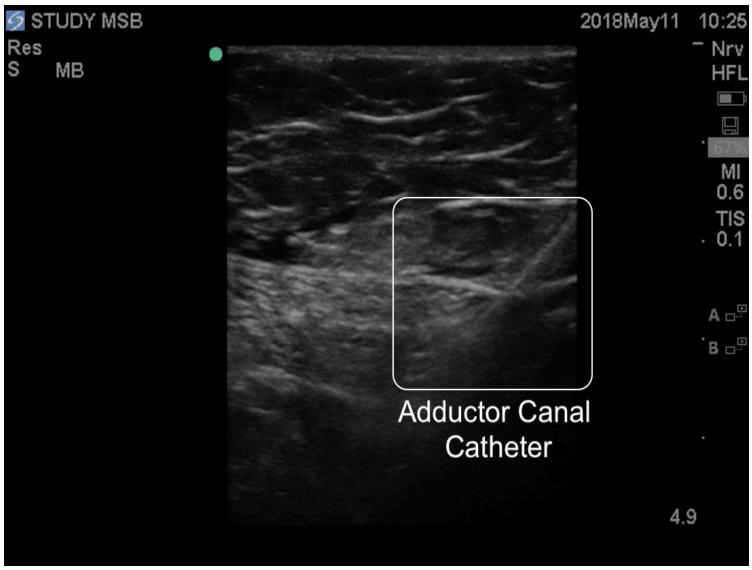


Figure 9: Continuous adductor canal catheter

5.6.1.3 Posterior Pericapsular injection (25mL bolus)

Following the previously described steps, a pre-injection scan is utilized to mark the site of injection and anaesthetized using lidocaine. Under ultrasound guidance, the Tuohy needle is inserted within close proximity of the medial femoral epicondyle, and 10 cm from the knee joint line. Once confirmation of needle tip placement using colour doppler, a bolus injection of 25mL of study drug is administered to the area between the posterior aspect of the femur and the popliteal artery (figure 10).

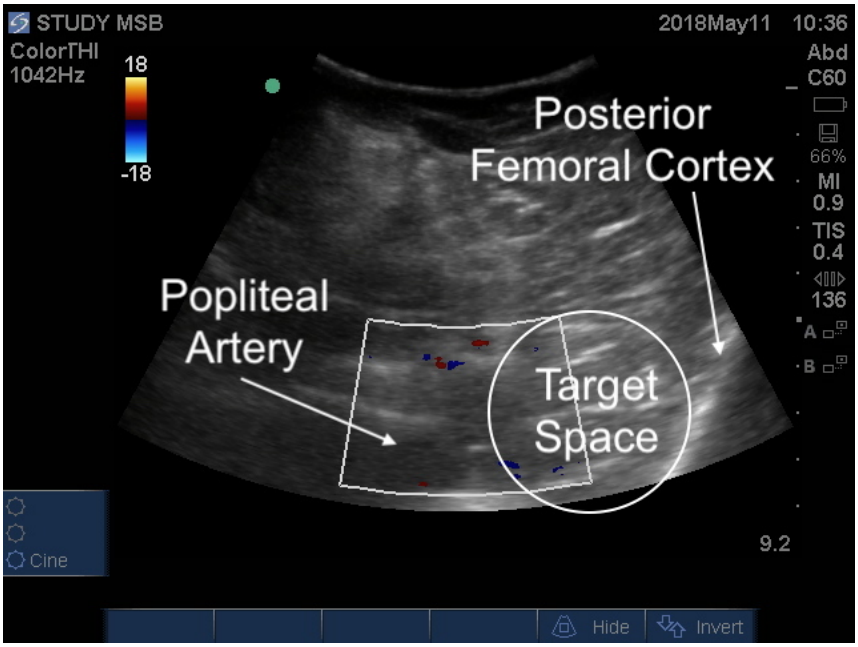


Figure 10: Ultrasound Image of the posterior pericapsular injection

5.6.1.4 Lateral Femoral Cutaneous Nerve (5mL bolus)

The final injection in our study control regional block is the lateral femoral cutaneous nerve (LFCN). It's identified by using the ultrasound to trace sartorius back to its origin at the anterior superior iliac spine. This is where the lacuna musculorum is located between the origin of sartorius and tensor fascia lata and is where the LFCN resides, and the injection site is marked and anaesthetized. The remaining 5mL of study

solution are injected within this area following needle tip position confirmation on ultrasound and concludes the motor sparing nerve block procedure (figure 11).

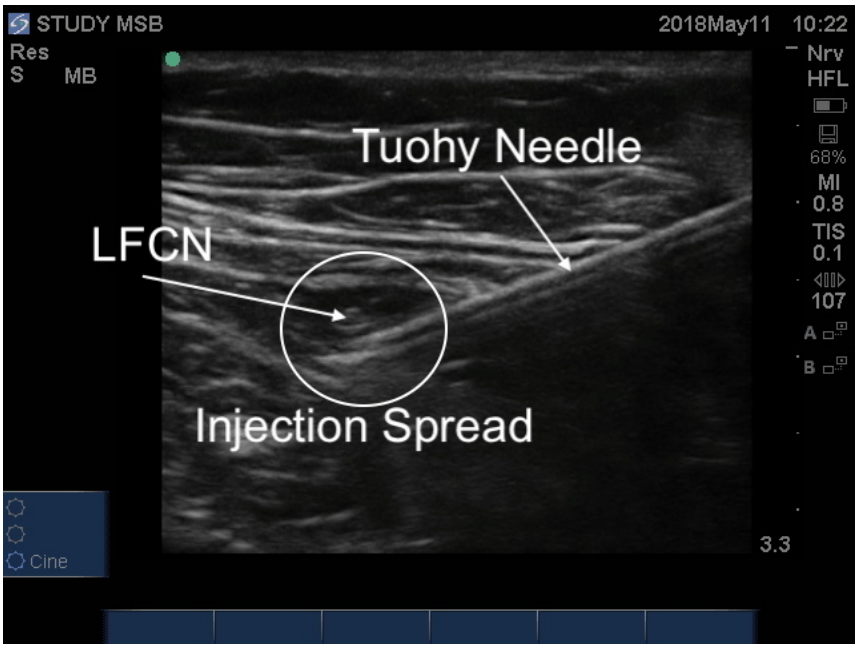


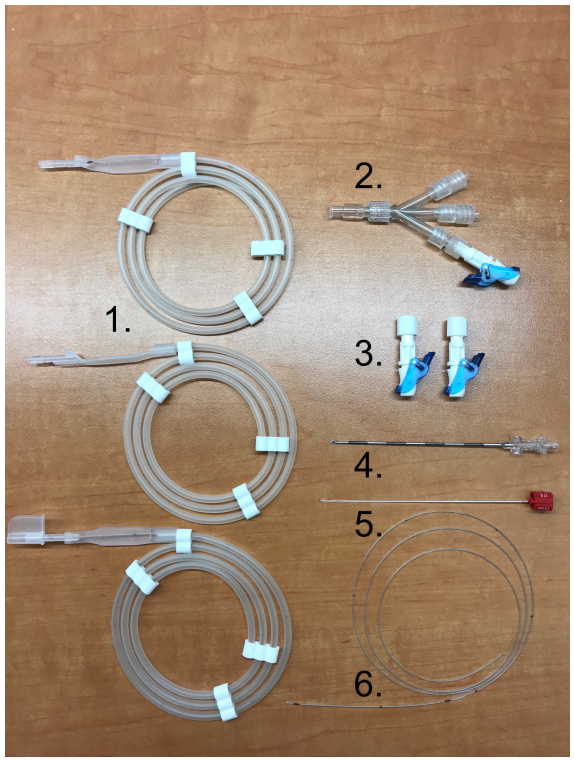
Figure 11: Ultrasound Image of the intermediate cutaneous nerve of the thigh injection

5.6.2 Periarticular Infiltration and Infusion Experimental Group:

Periarticular Infiltration and infusion (experimental group) is a regional anaesthetic method that is conducted intraoperatively by the surgical team. The local infiltration injection comes in a pre-made sterile solution provided by our center's operating room Pyxis. The solution is provided in a standard 110ml volume of 0.5% ropivacaine, 10mg of morphine, and 30mg of ketorolac. Toward the end of the case, following completion of the index procedure and preparation for surgical site closure, the surgeon injected variable volumes of infiltration anaesthetic throughout the knee joint within the exposed soft tissues.

Following infiltration of the knee, the next step was placement of the continuous infusion catheters, part of the periarticular infusion kit produced by Pajunk. These three, small gauge infusion catheters are uniquely constructed being 900mm in length total, with the most distal 75mm having 30 micro perforations 360-degrees around the

circumference to allow equal fluid distribution to the area. The rest of the kit includes three clamping adaptors to attach the catheters to the three-way splitter, as well as a Tuohy needle and stylus to allow for accurate catheter placement (figure 12).



Pajunk Periarticular Catheter Kit

Contents:

1. Catheter Sheath x 3
2. Three-way Connector x 1
3. Clamping adaptors x 3
4. Tuohy Needle x 1
5. Tuohy Needle Stylus x 1
6. Infiltralong Catheter x 3
   - -19Gx 900mm
   - -30 holes/75mm

Figure 12: Pajunk Periarticular Infiltralong Catheter Kit

Catheter placement is performed with the use of the seldinger technique, using the Tuohy needle to guide the flexible infusion catheters to their desired position. Prior to Tuohy needle insertion the placement is finalized by marking three points superiorly, from anterior to posterior (figure 13).

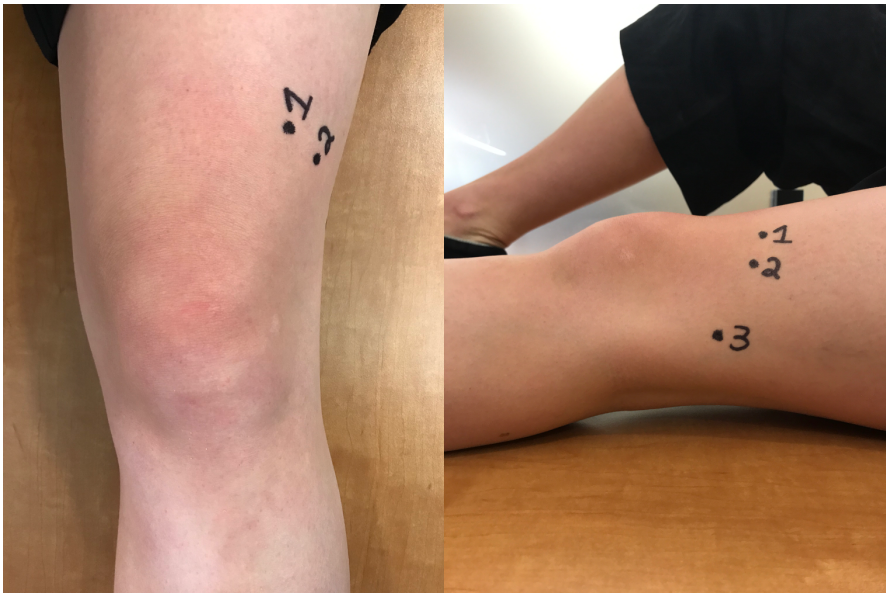


Figure 13: Catheter placement from anterior and lateral views

5.6.2.1 Subcutaneous Catheter:

Insertion site one is positioned approximately two inches superior and two inches lateral to the superior pole of the patella and is for placement of the subcutaneous catheter. The Tuohy needle is inserted, and the needle tip is identified under direct visualization within the subcutaneous space. A catheter, within its protective sheath, is fed through and pulled to the desired length internally, leaving four black markings visible externally (figure.8). Finally, the Tuohy needle is removed retrogradely, leaving only the catheter in situ.

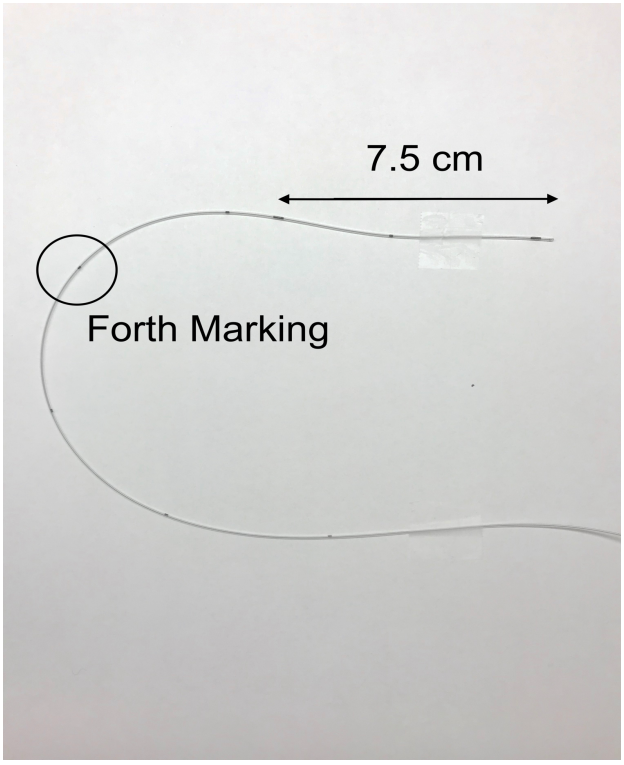


Figure 14: Infiltralong catheter markings and perforated section

5.6.2.2 Intraarticular Catheter:

Using the same direct visualization technique utilized for the subcutaneous catheter, the intraarticular catheter is placed at the second marked position, slightly more posterior to the subcutaneous insertion site prior to surgical closure of the arthrotomy. The catheter is then placed in the lateral gutter intraarticularly to allow unrestricted range of movement and reduce the rick of the catheter becoming lodged in between the articulating components.

5.6.2.3 Posterior Catheter Placement:

The posterior catheter uses a different method of placement, as it cannot be visualized directly once in situ. The catheter insertion sight is dictated by firstly palpating the lateral epicondyle of the distal femur, moving proximally past the metaphysis to the most distal portion of the diaphysis, approximately 3 to 5cm from the epicondyle. The Tuohy needle is inserted from lateral to medial directly perpendicular to the femoral shaft and once the needle comes into contact with the lateral cortex, is gently redirected posterior along the

surface of the cortex a further 2cm. Once the needle is in position, the stylus is removed and a 10ml syringe containing sterile saline is used to initially aspirate to ensure the needle tip is not intravascular. Once deemed safe, the saline bolus is delivered to create space for the final catheter and the syringe is removed to allow delivery of the catheter.

Once all three catheters are in position, their exposed ends were attached to the clamping adaptors and connected to the three-way splitter where the whole system is primed with sterile saline. Finally, the entry sites were sealed with dermabond and covered with a tegaderm dressing to reduce the risk of infection as well as protect the catheters from mistakenly being dislodged from their site.

5.7 Standardization of Study Groups:

Wanting to keep the two study populations as similar as possible, a number of standardized pre and post-surgical protocols were set. Beginning just after the time of admission on the day of surgery, patients, with a permitting medical status, received a pre-operative multimodal analgesic regimen consisting of 975mg Acetaminophen, 300mg Gabapentin, and 500mg Naproxen orally in the block room. The use of pre-operative non-steroidal anti-inflammatories as well as neuropathic analgesics has been shown to decrease post-operative pain and opioid consumption [69]. Prior to being transferred to the operating room for their procedure, a spinal anaesthetic was performed by and anesthetist under titrated sedation containing 15mg of hyperbaric bupivacaine with no intrathecal opioids. The initial bolus in both groups were also standardized containing 0.5% ropivacaine, 30mg Ketorolac, and 10mg of morphine, being delivered through either ultrasound guided injections pre-operatively in the MSNB group or through periarticular infiltration in the experimental group intraoperatively. 150mcg of Epinephrine were also added to the MSNB injection as per protocol in our previous study, where it was not included in the knee infiltration cocktail due to the risk of contamination of the previously described standard infiltration solution that is readily available in our operating room.

In terms of intra-operative surgical standardization, all patients underwent a primary total knee arthroplasty using one of two implant options; Depuy Attune or Stryker Triathlon. Cases were performed with the use of a tourniquet for a bloodless technique and the addition of patellar resurfacing during the procedure was left to the surgeon's judgement.

Post-operatively, the basal infusion in either group was commenced in the post-operative care unit with the use of a continuous ambulatory delivery device (CADD pump). The infusion drug administered was 0.2% ropivacaine, set at a basal rate of 8 milliliters per hour (lock-out of 8.1 milliliters), with the option of a patient-controlled bolus being removed. For breakthrough or uncontrolled post-operative pain, a standardized multimodal analgesic order-set consisting of 650mg Acetaminophen Q6h, Naproxen 500mg Q12h, Tramadol 50mg Q4h PRN, Hydromorphone Tablets 2-4mg Q3h PRN, and Hydromorphone Subcutaneous Injection 1mg Q3h PRN. Catheter removal was contingent on the patient meeting criteria for discharge, with readiness for discharge being dictated by our center's standard protocol.

A communication order made in the study's EMR order-set stated the Hold catheter or MSNB infusion at 6am post-operative day 2 or day of discharge, whichever comes sooner." This allowed for a more accurate assessment of pain prior to regional block removal and for possible post-operative day one discharge in patients who progressed through the post-op milestones more rapidly. Upon meeting criteria for discharge, the block catheters were then removed.

5.8 Outcome Measures:

The following outcomes were measured at various time-points depending on the type of data collected. Figure 15 is a time-line displaying the outcomes collected at various time-points.

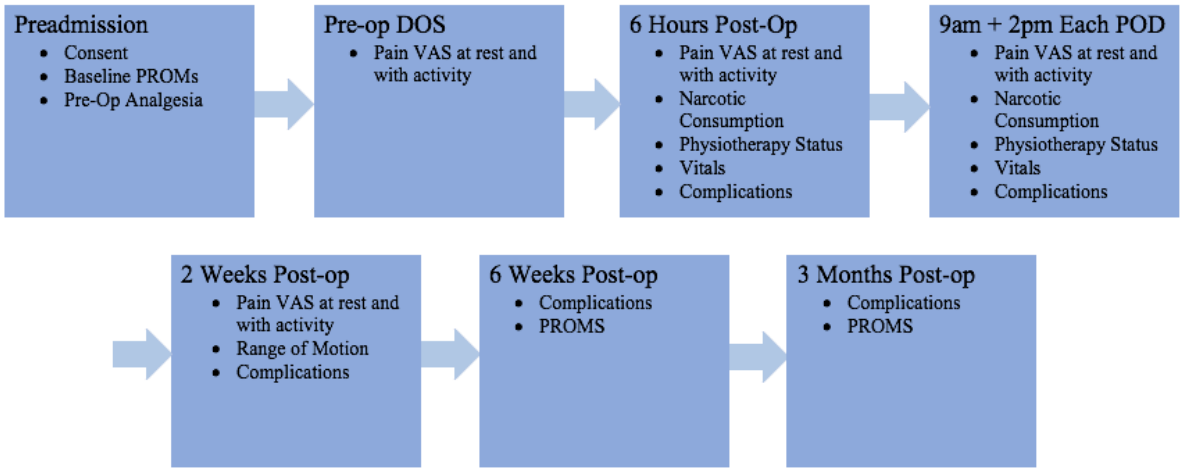


Figure 15: Timeline of outcome data collection

5.8.1 Primary Outcome Measure:

The primary outcome measure was set as time-to-discharge in this study. This was defined as the time at admission to the time of discharge. There are a variety of factors that can delay patient's early discharge following a total knee replacement. Poor pain control is a common cause to delay discharge but can also be a major component in other post-operative issues. Inadequate analgesia can lead to an increase in opioid related complications (Ileus/constipation, nausea/vomiting, delirium, sedation, respiratory depression), inability to perform physiotherapy exercises and milestones required for discharge, and cause patient to be unwilling to go home. All known complications suffered by inpatients were recorded to both ensure there weren't any major adverse events associated with one of the groups, and to be taken into consideration at the time of final analysis.

Readiness for discharge is dictated by our center's discharge protocol found below. The care team, specifically the attending surgeon/team resident and physiotherapist, assess and determine if patients have satisfactorily met these criteria.

Discharge Criteria:

1. Patient able to complete daily tasks such as get in and out of a chair or bed, get off and on the toilet, walk a suitable distance (30m) with proper walking aids without a time limit, and navigate an acceptable number of stairs.
2. Have no medical or surgical complications including urinary catheterization or need for blood transfusion
3. Acceptable pain relief (NRS = 5/10) without any need for intravenous analgesics.
4. No nausea/ vomiting; generalized weakness or dizziness.
5. Knee flexion of 90^0 is optional but preferred.

With these criteria, an effective regional anaesthetic technique must work to expedite the post-operative process by treating patient's pain, while reducing the risk of potentially discharge delaying complications and be cost-effective. With the ever-increasing cost of healthcare, exploring possible care options that reduce the inpatient stay of patients is important to the future of patient management following total knee arthroplasty.

5.8.2 Secondary Outcome Measures:

Numerous secondary outcomes were measured throughout the study period. This allowed for collection of possible confounders that could affect a patient's time to discharge, as well as ensure no significant functional differences occurred between the two groups.

5.8.2.1 Numeric Pain Rating Scale (NPRS):

A numeric pain scale was utilized in the study to assess patient's subjective pain levels both at rest and during activity. Activity was described as any major movement of or weightbearing on operative leg. The 11-point scale, measuring 0-10 (10 being the worst pain ever experienced) was assessed using a visual analogue scale (VAS). This model

has been verified by Williamson et al.[127] and was found to be highly sensitive, reliable, and easy to obtain. Pre-operative baseline scores were collected on the day of surgery before commencement of the spinal anaesthetic. VAS scores were collected post-operatively at six hours, and then again at 9am and 2pm during each inpatient post-operative day by a study assessor. Upon discharge, patients were instructed on the use of a pain dairy to chronical their own scores for four more post-discharge days.

5.8.2.2 Narcotic Consumption:

Narcotic consumption post-operatively was collected at six hours, 9 am and 2pm of each inpatient post-operative day, and during the four days post-discharge by patients through the pain dairy. The time, dose and frequency were recorded from the medication administration record available in the our EMR, as well as from the patient's pain diary. All narcotic medications were converted to morphine equivalence for comparison between the two groups.

5.8.2.3 Physiotherapy status:

Physiotherapy progress was recorded at the time of each assessment during the patient's inpatient stay. Patient's ability to perform physiotherapy and complications that inhibited their ability were documented. Progress was measured through range of movement by the staff physiotherapists. These measurements are involved in the criteria for discharge and can be affected by the efficacy of a patient's analgesic modality.

5.8.2.4 Complications/Adverse Events:

All complications, regardless of being directly, indirectly or not contributable to the surgical procedure were recorded. Information documented regarding the complication included the diagnosis, date, treatment administered, whether a delay in discharge occurred because of it, and the discharge day following successful management. Complications being monitored include the rates of myocardial infarction, deep venous thrombosis, pulmonary emboli, paralytic ileus, gastrointestinal bleed, new onset renal dysfunction, wound infection, as well as procedure specific complications such as dense

motor block in the MSNB group. This will allow us to control for a possible confounder in the final analysis.

5.8.2.5 Side Effects:

At the time of each inpatient visit as well as during assessment time points in the pain diary, side effects that were collected included the presence of nausea or vomiting as well as sedation. Patients used a five-point evaluation scale for nausea with none, mild, moderate, severe, extreme as options. For sedation, a 5-point scale of 0-5 was utilized, with 0 being not sedated, to 5 being nearly unable to stay awake.

5.8.2.6 Vital Sign Data:

During in-patient data collection visits, research staff collected data pertaining to the most recent vital signs recorded by the nursing staff, specifically looking at respiratory rate, pulse oximetry as well as whether the patient was breathing on supplementary oxygen or room air. This was to assess for the presence of respiratory depression associated with narcotic medications being used for breakthrough pain in the post-operative multimodal analgesic order set.

5.8.3 Functional outcomes:

Functional outcomes following total joint arthroplasty are an important and expected measurement in trials. A procedure that causes a significant deviation in the expected functional outcomes of patients should not be considered for implementation into practice.

5.8.3.1 WOMAC:

The Western and McMaster Universities Osteoarthritis Index is a patient reported outcome measure that assesses symptoms and physical disability caused by osteoarthritis of the hip or knee. There are a number of tailored questions that are designed to evaluate three specific categories including pain (five questions, score 0-20), stiffness (two questions, score 0-8), and subjective physical function (17 questions, score 0-68). The three scores create individual numeric values for each of the three

dimensions as well as a total score that correlates with the severity of the patient's symptoms. The version used in our study is called Likert version, which uses a scale of none (0), mild (1), moderate (2), severe (3), and extreme (4), with a higher score indicating a worse symptom/functional state. The WOMAC also allows healthcare providers a means of evaluating clinically important changes in health status over time following administration of an intervention[128].

The WOMAC is a validated tool that when applied to total knee replacement trials, can provide reliable and sensitive outcome data. A literature review of 43 articles conducted by McConnell et al.[129] found that the internal consistency for pain, stiffness, and physical function measured 0.86, 0.90, and 0.95 respectively.

In our study, it was decided a baseline WOMAC score would be collected at the pre-admission appointment, with post-operative reassessments occurring at the 6-week and 3-month follow-up visits.

5.8.3.2 The New Knee Society Score:

The new Knee Society Score (KSS) is a combined subjective (patient) and objective (clinician) outcome measurement tool. The original Knee Society Clinical Rating Tool, developed in 1989, allowed for the objective measurement by healthcare providers of a patient's functional abilities both pre and post-operatively following TKA. The validity of the original tool diminished over time with the greater importance of patient's expectations, demands, and functional requirements being realized[130].

The new Knee Society Scoring system was developed and validated in 2011 to take these considerations and incorporate them into a more contemporary model and includes both a pre-operative and post-operative version. A combination of patient reported outcomes as well as a physical and radiographic assessment carried out by the clinician. For the functional component of the survey scores are created in four specific dimensions including symptoms, satisfaction, expectations, and functional activity[130].

The objective score and purely clinician assessed component includes physical examination findings, and radiographic components. These questions include a VAS pain score, range of movement, presence of flexion contracture (points deducted depending on degree), presence of extension lag (points deducted depending on degree), ligamentous stability, and radiographic alignment.

5.8.3.3 SF-12 Health Survey:

The Short Form Survey 12, or SF-12, is a condensed version of SF-36 health survey that aims to evaluate a patient's personal view on the status of their over-all health, both mental and physical. The SF-12 is a validated, reliable and responsive patient reported outcome measure[131]. The content of the questions covers physical function (two questions), bodily pain (one question), general health perceptions (one question), vitality (one question), social functioning (one question), emotional problems interfering with social activities (two questions), and finally, general mental health (two questions)[131]. The scores from these questions are then applied to an overall SF-12 physical and SF-12 mental health scores, with a range of zero (worst possible health state) to 100 (best possible health state).

Again, a baseline score was taken at the pre-admission appointment, with post-operative values coming from the 6-week and 3-month follow-up visits.

5.9 Sample Size:

In a case study conducted by Kerr and Kohan et al.[101] involving 325 patients, it was found that the overnight discharge rate with local wound infiltration was 71%. We expect a 30% improvement in the overnight discharge rates for patients who receive a motor sparing nerve block.

A formal equality sample size calculation was performed with a two- sided alpha error rate of 0.05, with statistical power being set at 80%. e

5.10 Data Analysis:

We analyzed all data from patients with an intention to treat analysis using SPSS Version.24 (IBM Corp, Armonk, NY). For patient demographic characteristics, we employed the use of descriptive statistics, comparing the means and reporting the standard deviations for continuous variables (age, height, weight, BMI), and proportions for nominal variables[132].

For the analysis of our primary outcome, time to discharge, we used a Mann-Whitney U Analysis with Bonferroni correction due to the inherent lack of data normality. The dependent variable was time to discharge and the group allocation (MSNB or LIA and infusion) was the independent variable. For secondary outcomes, we utilized a multivariate analysis of covariance (MANCOVA) to compare VAS pain scores at rest and activity at the various data collection time points. The dependent variable was VAS score, the group allocation (MSNB or LIA and infusion) the independent variable, with baseline VAS scores (rest and activity) served as covariates[132,133].

Multivariate analysis of variance (MANOVA) was performed for narcotic consumption (in morphine equivalence), respiratory rate and oxygen saturation to compare the groups at each inpatient time point. An analysis of covariance (ANCOVA) was performed for patient reported outcome measures (SF-12, WOMAC, KSS), as well as physiotherapy range of movement. Baseline WOMAC, SF-12, KSS scores, and preoperative range of movement were used as covariates respectively. If data was found to be not normally distributed, we used a Mann-Whitney U statistical test to compare the two groups, and a Bonferroni correction was utilized to correct for multiple comparisons[132].

We set significance at $p<0.05$ and reported the unadjusted mean with 95% confidence intervals (CI) in figures. In the tables and text, the adjusted mean (means adjusted to the presence of the covariate) with standard error (SE) was stated as well as the adjusted mean difference with 95% CI. For missing data points, the last outcome carried forward method was utilized[132].

Chapter 6

6 Results

6.1 Participant Flow

Following pre-screening using our hospital's electronic medical record, patients were approached through the preadmission clinic prior to surgery to be assessed for study eligibility. Participant flow through the study is demonstrated in Figure 16. From October 2017 to May 2018, a total of 422 patients were screened for the study. Of this group, 72 patients were randomized, with 75% (n=54) successfully enrolled in the trial. In the motor sparing nerve block group (MSNB), there were 29 patients and in periarticular Infiltration and infusion group (LIA and infusion) there were 25. Demographic data is provided in Table 7. All 54 patients had inpatient VAS, physiotherapy, and narcotic consumption data, with 42 patients reaching the end of the trial (3-months) at the time of analysis. Study power was not achieved, and the following results are from an interim analysis.

Patient ineligibility was determined utilizing previous medical documentation or during the preadmission interview. The most common reasons for exclusion were chronic pain and pre-operative narcotic use (n=78), enrollment in another study (n=65), declining to participate (n=45) and BMI >45 (n=36).

Twenty-five percent (n=18) of the enrolled patients were excluded following randomization. Reasons included violation of study protocol (n=1), undisclosed allergy to a study drug (n=1), non-disclosure of pre-operative narcotic abuse (n=1) and contraindicated to MSNB due to recent anticoagulation (n=1). Other reasons were changed date of surgery (n=1), failure of block catheter placement (n=2), two patients dropped out of the study prior to surgery, and unknown chronic renal impairment (n=2). Seven patients were unable to participate in the study due to an unforeseen nationwide supply shortage of ropivacaine, resulting in a study hiatus. No study participants required conversion from spinal anaesthetic to general anaesthetic intraoperatively.

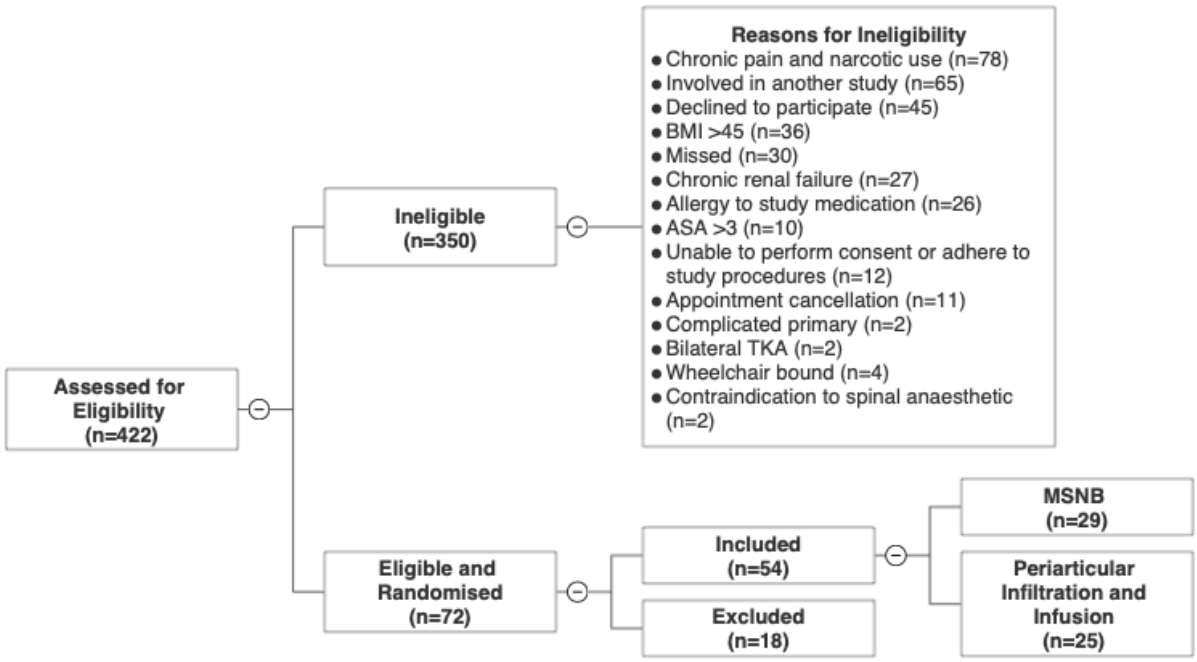


Figure 16: Participant flow through the study

Table 7: Patient Demographics

Characteristic	Motor Sparing Knee Block (n=29)	Periarticular Infiltration and Infusion (n=25)
Male, n (%)	n= 14 (48%)	n= 13 (52%)
Mean Age ± SD, y	68 ± 8.37	65 ± 9.56
Mean Height ±SD, cm	169 ± 10.07	169 ± 10.66
Mean Weight ± SD, kg	90 ± 18.06	91 ± 18.55
Mean BMI ± SD, kg/m^2	31.85 ± 5.42	31.96 ± 6.02
Operative Knee, Right	n=14 (48%)	n=11 (44%)
ASA Status One Two Three	Mean= 2.55 ± 0.50 n=13 (45%) n=16 (55%)	Mean= 2.32 ± 0.56 n=1 (4%) n=15 (60%) n=9 (36%)

Pre-Operative Diagnosis Osteoarthritis Inflammatory	n=28 (97%) n= 1 (3%)	n=24 (96%) n= 1 (4%)
Previous Surgery on ipsilateral knee (total) Arthroscopy Osteotomy Ligament reconstruction	n=6 (21%) n=2 n=2 n=2	n=12 (48%) n=11 n=1

SD = standard deviation, BMI = body mass index, ASA = American Society of Anaesthesiologists physical status classification system

6.2 Primary Outcome Measure:

6.2.1 Time to Discharge from Hospital:

There were no statistically significant differences in the times to discharge between the motor sparing nerve block and the periarticular infiltration and infusion groups (p= 0.47). The mean time to discharge for the MSNB group was 2.57 days (SD ± 1.0), while the LIA and infusion group was 2.5 days (SD ± 1.25). Both groups had similar mean time to discharge and are both skewed towards a short duration in hospital as demonstrated in the histograms below (figure 17).

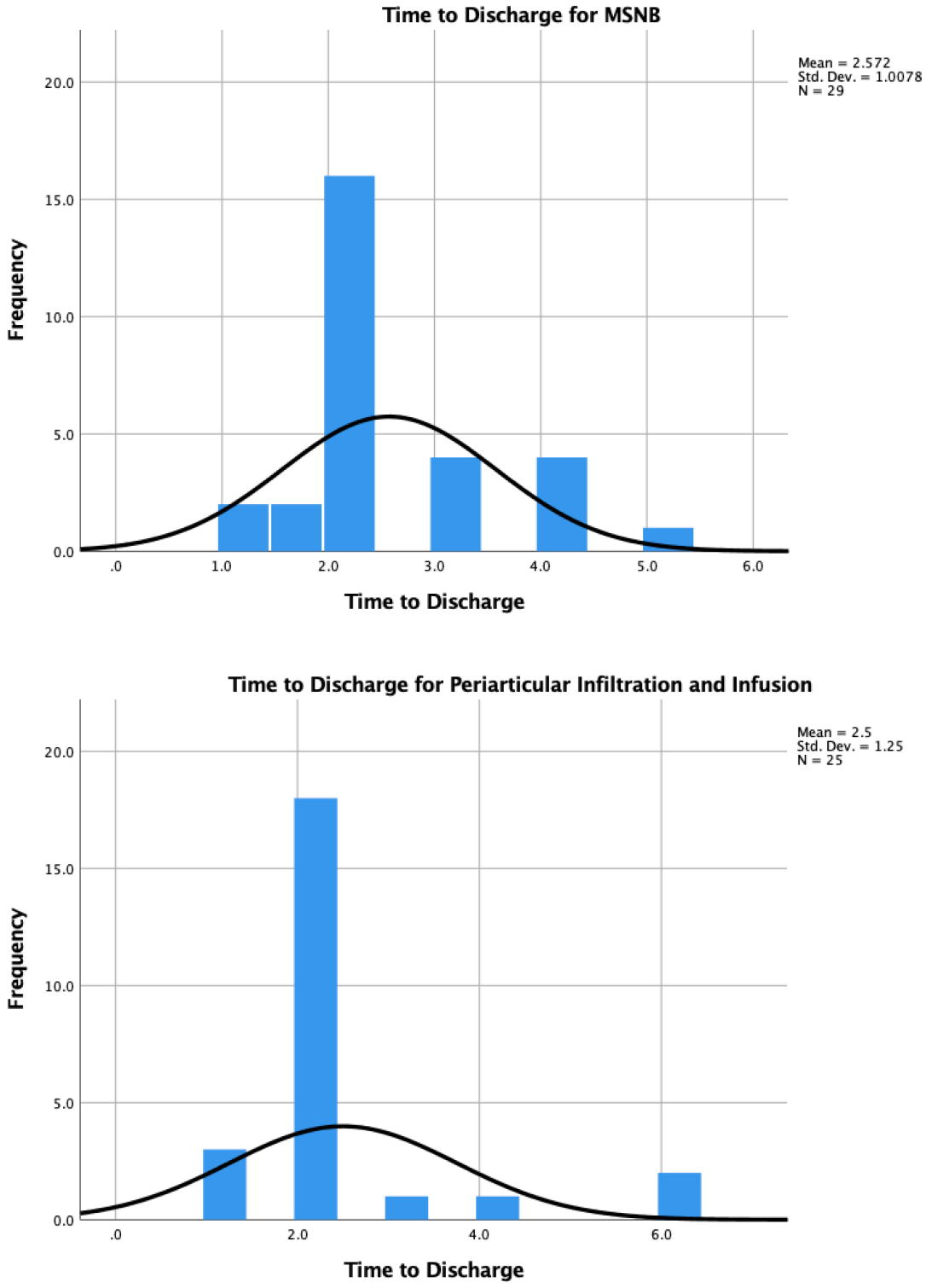


Figure 17: Distribution of time to discharge from hospital for MSNB and periarticular infiltration and infusion

6.3 Secondary Outcome Measures:

6.3.1 Visual Analogue Scale Pain Scores

Visual analogue scale (VAS) pain scores were collected for both groups at each inpatient time point as well as following discharge through the pain diaries. VAS scores at rest as well as with activity were documented individually. Data was collected at six hours post-op and for six post-operative days, twice daily, for a total of 13 collection points.

6.3.2 Visual Analogue Scale at Rest:

Using the pillai's trace test with MANCOVA analysis, there was not a significant difference for VAS scores at rest between the two groups, MSNB and LIA, when controlling for pre-operative VAS rest scores ($V=0.3$, $F(13,39) = 1.28$, $p=.266$). Table 8 displays the adjusted means for both groups at each time point. Separate univariate ANCOVAs did show a significant difference in VAS rest pain scores between the adjusted means at 6 hours post-op ($F(2, 51) = 4.46$, $p= 0.016$) with the MSNB group having superior analgesia less. No other time points were statistically significant. The covariate for pre-op VAS score at rest did not have a significant effect on the outcome (post-op pain at rest) $V=0.27$, $F(13, 39) = 10.9$, $p=0.39$. Figure 18 graphically displays the unadjusted VAS score means over the assessment period.

Table 8:VAS scores at rest (adjusted means, bold indicates significant time points)

Time Point Post-op	MSNB mean ± SE	LIA mean ± SE	Adjusted Mean difference (95% CI)	p-value
6 hours	**2.09 ± 0.45**	**3.97 ± 0.48**	**-1.88 (-3.21 to -.551**	**p=0.007**
POD1 9am	3.30 ± 0.42	4.09 ± 0.45	-0.78 (-2.03 to 0.47)	p=0.21
POD1 2pm	3.02 ± 0.39	3.66 ± 0.41	-0.65 (-1.80 to 0.51)	p=0.26
POD2 9am	2.71 ± 0.33	1.99 ± 0.36	0.79 (-0.19 to 1.78)	p=0.11
POD2 2pm	2.81 ± 0.35	2.14 ± 0.38	0.67 (-0.37 to 1.72)	p=0.20
POD3 9am	2.79 ± 0.36	2.64 ± 0.39	0.15 (-0.84 to 1.15)	p=0.75
POD3 2pm	2.76 ± 0.36	2.61 ± 0.39	0.15 (-0.912 to 1.21)	p=0.77
POD4 9am	2.67 ± 0.41	2.67 ± 0.44	0.00 (-0.1.6 to 1.07)	p=0.99
POD4 2pm	2.83 ± 0.38	2.76 ± 0.41	0.06 (-0.15 to 1.28)	p=0.91
POD5 9am	2.81 ± 0.37	2.46 ± 0.40	0.36 (-0.78 to 1.48)	p=0.52
POD5 2pm	3.05 ± 0.37	2.47 ± 0.40	0.62 (-0.89 to 1.1)	p=0.26
POD6 9am	2.75 ± 0.34	2.85 ± 0.36	-0.11 (-1.1 to 0.88)	p=0.83
POD6 2pm	2.79 ± 0.34	2.29 ± 0.36	0.50 (-0.5 to 1.5)	p=0.31

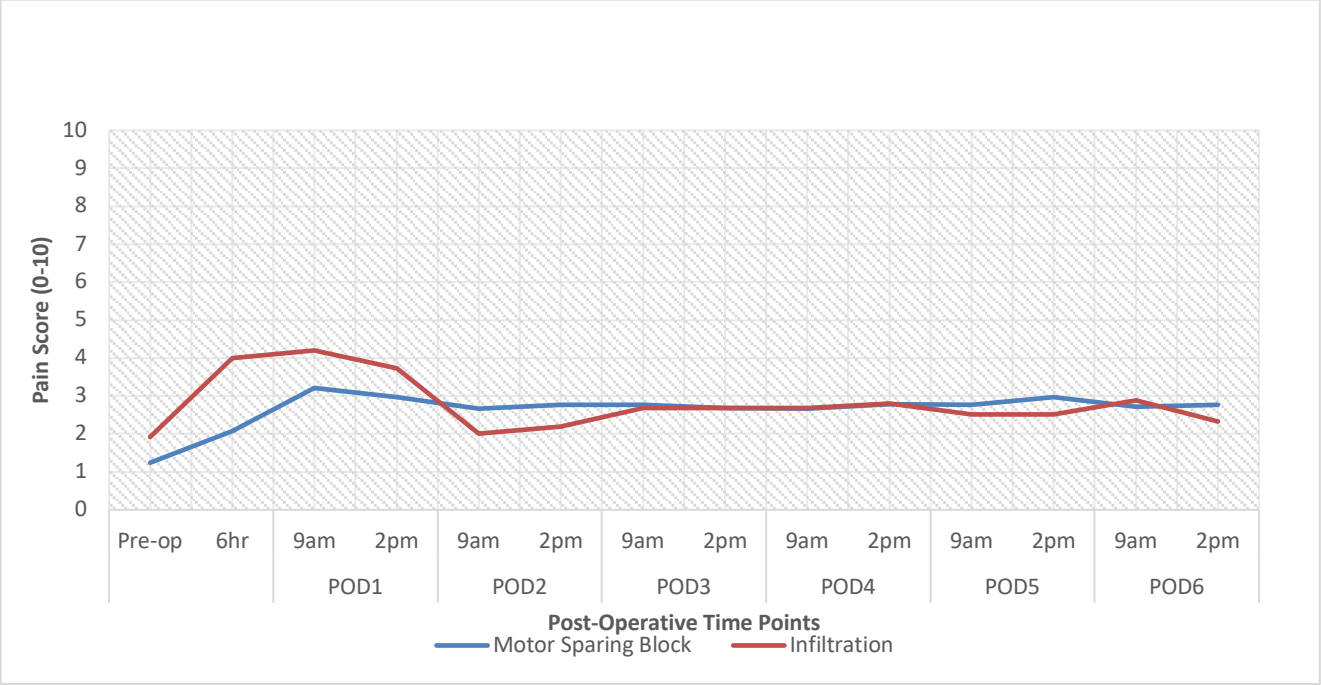


Figure 18: VAS scores at rest between MSNB and LIA and infusion groups (unadjusted means)

6.3.3 Visual Analogue Scale with Activity:

Following MANCOVA analysis and pillai's trace test, there was not an overall significant treatment effect between MSNB and periarticular infiltration, when controlling for pre-operative activity VAS pain scores on the reported VAS for pain during activity (V= 0.37, F (13,39) = 1.76, p=0.086). Table 9 displays the adjusted means for both groups at each time point. Separate univariate ANCOVAs did show a significant difference in VAS activity scores between the adjusted means at three time points; 6 hours post-op (F (2, 51) = 9.03, p< 0.001); 2pm Post-op day (POD) 1 (F (2, 51) = 8.59, p= 0.001); 9am POD 2 (F (2,51) = 4.24, p= 0.02). MSNB had superior analgesia at 6 hours post-op and 2pm POD 1, but LIA and infusion was superior at 9am POD 2. No other time points were statistically significant. The covariate for pre-op VAS score during activity did have a significant effect on the post-op VAS scores (V=0.40, F (13, 39) = 2.05, p=0.04). Figure 19 graphically displays the unadjusted means over the assessment period.

Table 9: VAS scores with Activity (adjusted means, bold indicates significant time points)

Time Point Post-op	MSNB mean ± SE	LIA and Infusion mean ± SE	Adjusted Mean difference (95% CI)	p-value
6 hours	**3.34 ± 0.46**	**5.87 ± 0.49**	**-2.48 (-3.84 to -1.126)**	**p=0.001**
POD1 9am	6.29 ± 0.41	7.03 ± 0.44	-0.74 (-0.48 to 1.95)	p=0.22
POD1 2pm	**5.97 ± 0.37**	**7.23 ± 0.40**	**-1.27 (-2.35 to -0.85)**	**p=0.02**
POD2 9am	**5.84 ± 0.35**	**5.35 ± 0.38**	**0.49 (-0.55 to 1.53)**	**p=0.34**
POD2 2pm	5.29 ± 0.43	5.27 ± 0.46	0.02 (-1.24 to 1.27)	p=0.9
POD3 9am	5.34 ± 0.44	5.66 ± 0.48	0.08 (-1.23 to 1.38)	p=0.90
POD3 2pm	5.36 ± 4.49	5.74 ± 0.47	-0.39 (-1.68 to 0.92)	p=0.56
POD4 9am	5.02 ± 0.47	5.34 ± 0.50	-0.31 (-1.70 to 1.08)	p=0.65
POD4 2pm	5.17 ± 0.49	5.13 ± 0.53	0.04 (-1.38 to 1.49)	p=0.95
POD5 9am	5.46 ± 0.48	5.12 ± 0.51	0.32 (-1.08 to 1.72)	p=0.64
POD5 2pm	5.59 ± 0.49	5.08 ± 0.52	0.46 (-0.97 to 1.89)	p=0.51

POD6 9am	5.24 ± 0.49	5.20 ± 0.52	0.04 (-1.37 to 1.45)	p=0.95
POD6 2pm	4.93 ± 0.47	5. 04 ± 0.51	-0.11 (-1.50 to 1.27)	p=0.87

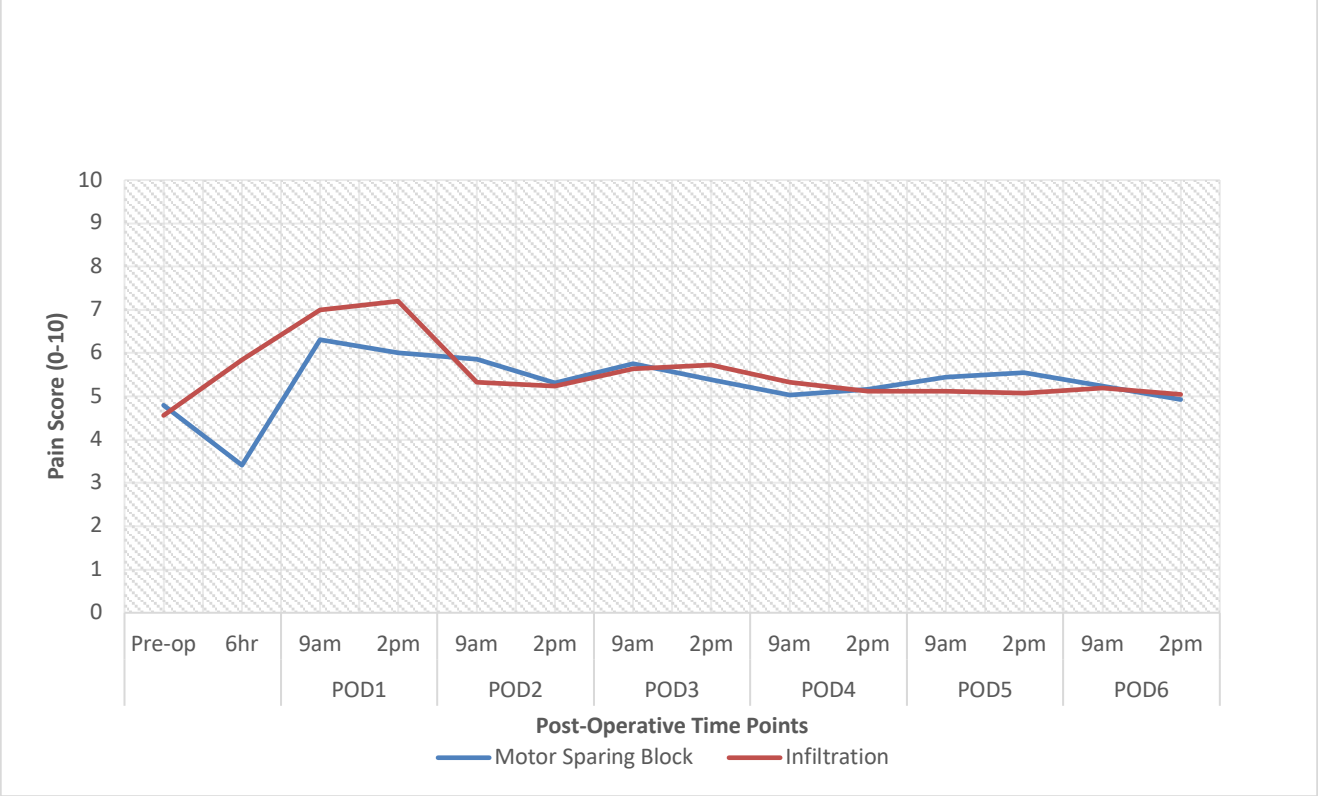


Figure 19: VAS scores during activity between MSNB and LIA and infusion groups (unadjusted means)

Below, Figures 20 and 21 combine the rest and activity VAS unadjusted means for each group to graphically display the magnitude of difference between the two scores at each time point.

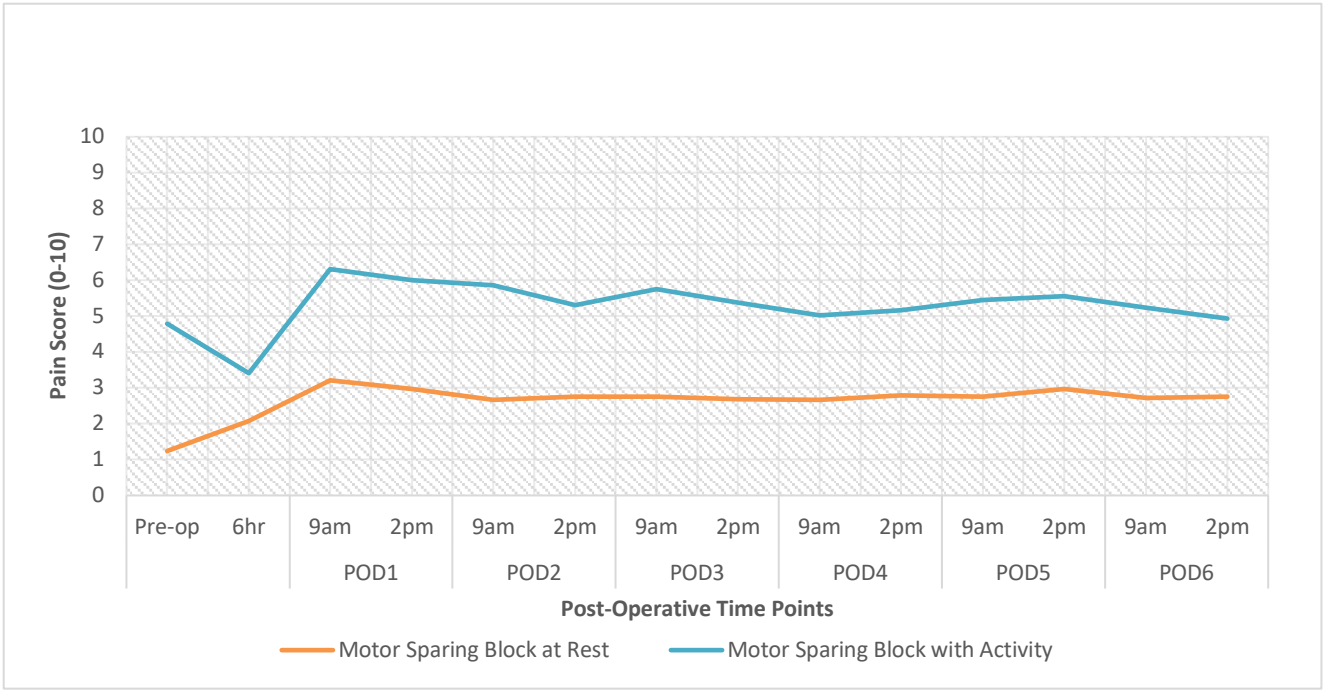


Figure 20: MSNB VAS scores at rest and during activity (unadjusted means)

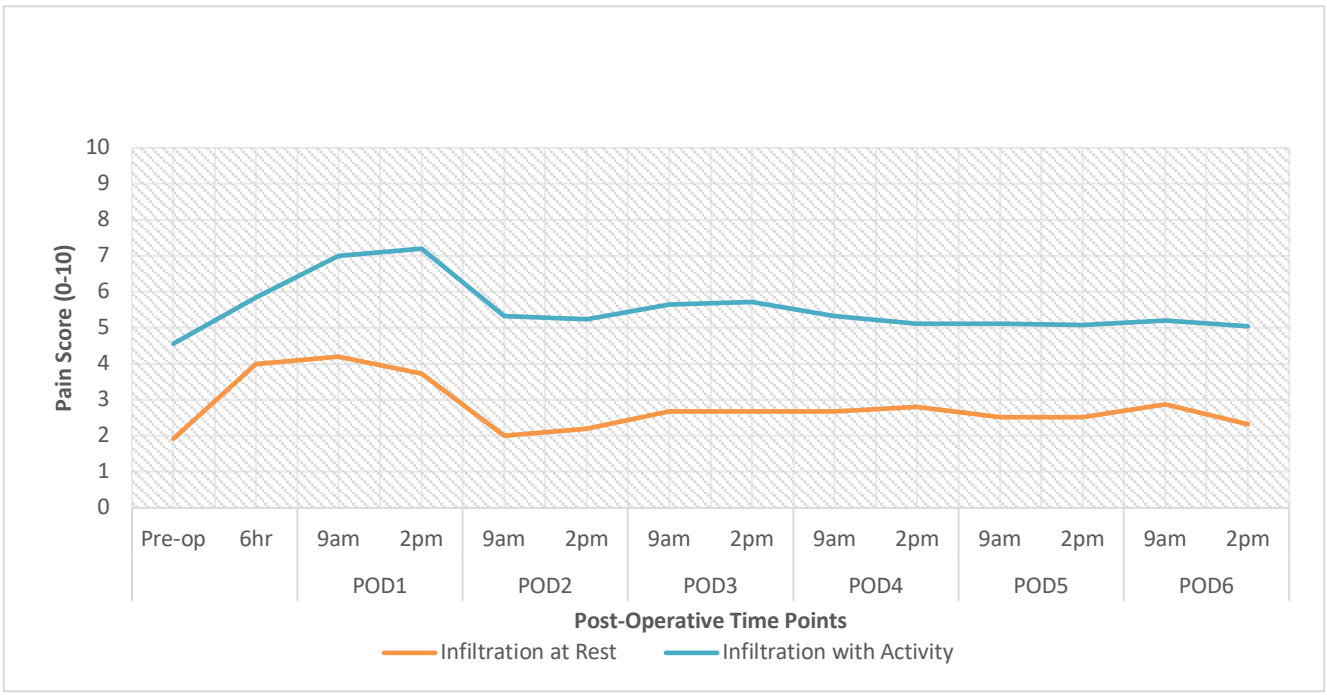


Figure 21: LIA and Infusion VAS scores at rest and during activity (unadjusted means)

6.3.4 Narcotic Consumption:

Inpatient narcotic consumption between time points was converted to morphine equivalence and the groups were compared (figure 22). There was no overall statistically significant difference in narcotic consumption between the two groups (pillai's trace V=0.073, F (5, 48) = 0.76, p= 0.59). There were also no significant differences at any of the time points between group unadjusted means (Table 10).

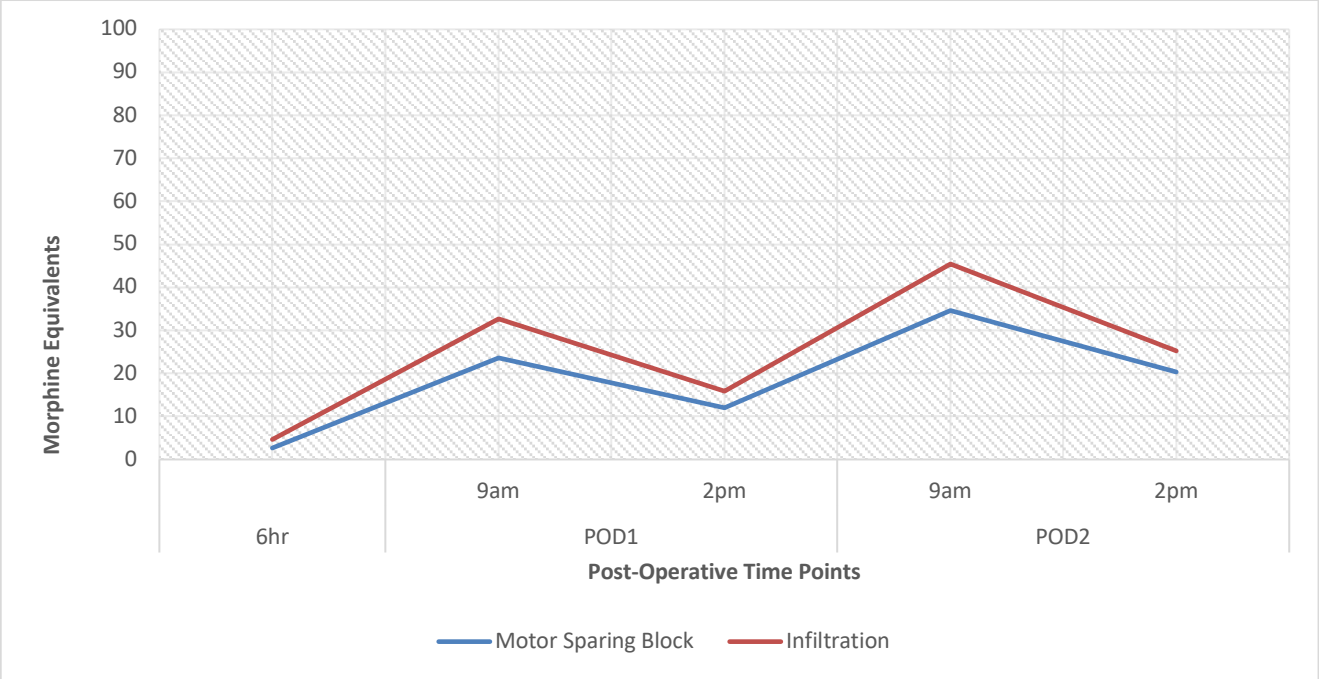


Figure 22: Morphine Equivalence (unadjusted means)

Table 10: Narcotic consumption in morphine equivalents (unadjusted means)

Time Point Post-op	MSNB mean ± SE	LIA and Infusion mean ± SE
6 hours	2.66 ± 1.17	4.64 ± 1.26
POD1 9am	23.66 ± 4.50	32.72 ± 4.85
POD1 2pm	12.00 ± 1.98	15.84 ± 2.13
POD2 9am	34.621 ± 5.14	45.440 ± 5.54
POD2 2pm	20.310 ± 4.35	25.200 ± 4.69

6.3.5 Side Effects:

6.3.5.1 Nausea:

Nausea is a common side effect as a result of narcotic use and was quantitatively assessed using a 0-4 numeric scale (0=none, 1=mild, 2=moderate, 3=severe, 4= extreme). There was no significant overall difference in nausea scores between treatment groups during the 6-day assessment period (p=0.21) (figure 23).

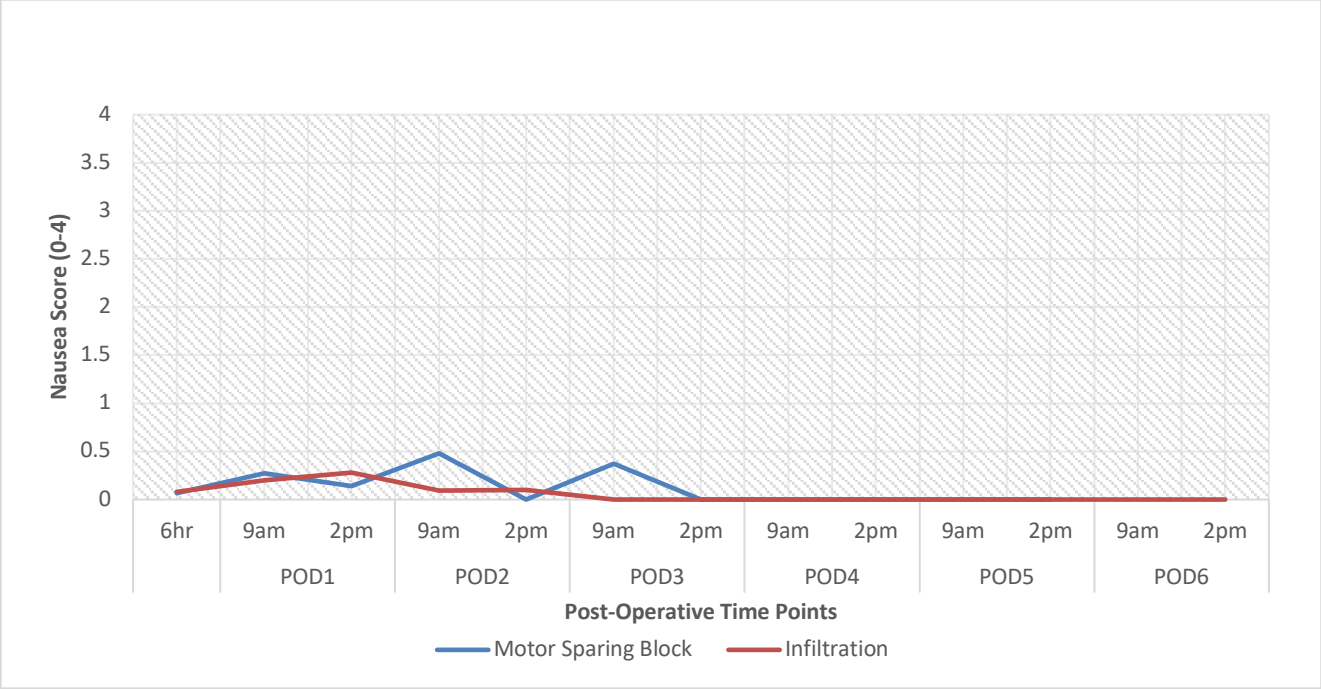


Figure 23: Nausea scores (unadjusted means)

6.3.6 Inpatient Respiratory Rate and Oxygen Saturation:

Patient vitals were collected at each post-operative timepoint to ensure there were no significant respiratory side effects because of large quantities of narcotic medications.

There were no statistically significant differences in respiratory rate (p=0.54) and oxygen saturation (p=0.67) between groups during the in-patient stay.

6.3.7 Physiotherapy:

While patients were in hospital, the ability to perform physiotherapy was noted by documenting the time point they had successfully performed physiotherapy by. There was no statistically significant difference (p=0.49) between groups in their ability to begin physiotherapy (means ± SD, time point; MSNB 2.07 ± 1.13, LIA and infusion 1.96 ± 0.98).

Range of movement (ROM) post-op was analyzed using two different outcomes, one being first ROM measured during physiotherapy and the other best achieved ROM while in hospital. Pre-operative ROM served as the covariate to control for baseline differences. There was no statistically significant difference in first measured ROM between groups post-operatively ($F(2,51) = 1.51$, $p = 0.23$). There also was no significant difference between groups comparing best achieved ROM while in hospital ($F(2, 51) = 1.98$, $p = 0.15$).

6.3.8 Two-week Follow-up Data:

6.3.8.1 Vas Pain Scores:

VAS rest and activity scores were collected at the 2-week post-operative visit. The pre-operative VAS scores were used as a covariate during analysis. There were no statistically significant differences in VAS scores at two weeks post-op during rest ($F(2, 51) = 0.535$, $p = 0.59$) or activity ($F(2, 51) = 1.51$, $p = 0.23$). Table 4 displays adjusted means to the covariate for each group.

Table 11: VAS score adjusted means at two weeks

VAS Score	MSNB mean ± SE	LIA and Infusion mean ± SE
Rest	2.39 ± 0.36	2.15 ± 0.39
Activity	4.12 ± 0.40	4.1 ± 0.44

6.3.8.2 Range of Movement:

There was no statistically significant difference in range of movement between groups at 2-weeks post-op after controlling for pre-operative ROM ($F(2, 51) = 1.41$, $p = 0.25$).

6.3.9 Patient Reported Outcome Measures:

Patient reported outcome measures including 12-item short-form survey (SF-12), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Society Score (KSS) were collected pre-op and again at 6-weeks and 3-months post-op. Data that was found to be not normally distributed prior to analysis included pre-op SF-12, Objective Knee Indicators, 6-week KSS symptoms, and 3-month KSS symptoms, and Objective Knee Indicators. Only one data point was found to be statistically significant. The KSS Expectations subsection was statistically significant between groups at the 6-week post-operative assessment ($F(2, 51) = 4.78$, $p = 0.012$). All other outcome measures at both the 6-week and 3-month post-operative timepoints were not significant. The adjusted means are reported below for SF-12 (table 12), WOMAC (table 13), and KSS (table 14).

Table 12: SF-12 patient reported outcome data

Time Point	SF-12 Component	MSNB mean ± SE	LIA and Infusion mean ± SE	Sig.
Pre-op	SF-12 Mental	55.60 ± 1.50	52.79 ± 1.88	p= 0.07
	SF-12 Physical	33.73 ± 1.91	36.91 ± 1.80	p= 0.20
6-week	SF-12 Mental	53.49 ± 1.6	53.90 ± 1.72	p=0.86
	SF-12 Physical	33.80 ± 1.51	35.44 ± 1.5	p=0.43
3-month	SF-12 Mental	56.19 ± 1.34	54.79 ± 1.44	p=0.48
	SF-12 Physical	39.86 ± 1.65	41.45 ± 1.78	p= 0.548

Table 13: WOMAC Total patient reported outcome data

Time Point	MSNB mean ± SE	LIA and Infusion mean ± SE	Sig.
Pre-op	51.42 ± 3.64	56.63 ± 3.69	p=0.277
6-week	67.23 ± 2.20	65.01 ± 2.37	p=0.499
3-month	73.23 ± 2.65	71.40 ± 2.85	p= 0.64

Table 14:KSS patient reported outcome data (bold indicates significant time point)

Time Point	KSS Component	MSNB mean ± SE	LIA and Infusion mean ± SE	Sig.
Pre-op	Symptoms	15.52 ± 0.80	18.04 ± 1.07	p= 0.13
	Expectations	13.89 ± 0.26	12.56 ± 0.61	p= 0.06
	Satisfaction	15.45 ± 1.56	19.48 ± 1.79	p=0.07
	Functional Activity	38.69 ± 3.12	42.0 ± 3.23	p= 0.58
	Objective Knee Indicators	35.89 ± 3.38	43.64 ± 4.21	p=0.54
6-week	Symptoms	21.66 ± 0.86	21.88 ± 4.74	p=0.48
	Expectations	**9.81 ± 0.52**	**9.62 ± 0.56**	**p = 0.01**
	Satisfaction	24.785 ± 1.47	25.13 ± 1.5	p=0.88

	Functional Activity	48.85 ± 2.81	52.69 ± 3.03	p= 0.36
	Objective Knee Indicators	63.22 ± 1.81	65.30 ± 1.95	p= 0.443
3-month	Symptoms	22.97 ± 0.873	22.88 ± 0.74	p=0.30
	Expectations	10.15 ± 0.58	10.11 ± 0.567	p=0.15
	Satisfaction	30.08 ± 1.59	27.38 ± 1.71	p= 0.26
	Functional Activity	61.07 ± 2.90	61.15 ± 3.13	p= 0.98
	Objective Knee Indicators	64.20 ± 2.99	65.92 ± 2.16	p=0.18

6.3.10 Adverse Events and Complications:

Throughout the course of the trial adverse events and complications were recorded during patient's in-hospital stay and follow-up interviews. There was a total of eight significant adverse events that caused a delay in discharge, three in the MSNB group and five in the LIA and infusion group (table 15).

Table 15: Significant adverse events during study period

Complication	Group	Treatment	Delay in Discharge
Foot drop	MSNB	Block cessation	1 day
Foot drop	LIA and Infusion	Block cessation	1 day
Quadriceps Weakness	MSNB	Block cessation	2 days

Quadriceps Weakness	LIA and Infusion	Block cessation	4 days
Pulmonary Embolism	MSNB	Therapeutic Anticoagulation	3 days
Catheter Site Abscess	LIA and Infusion	Spontaneous drainage, no septic arthritis	No delay, noted at two-week follow-up
Anaesthetic Toxicity	LIA and Infusion	Block, cessation and supportive management	No delay
Urinary Retention	LIA and Infusion	Supportive management	No delay

Inadequate analgesia was the cause for delayed discharge in three MSNB patients (range, 1-2 days), and two LIA and infiltration patients (range, 1-4 days). Other complications were less debilitating and did not inhibit discharge. In the MSNB group, one patient's block catheter occluded with blood, one patient's catheter was accidentally dislodged from the entry site during physiotherapy, and one patent's catheter leaked significantly. The management for each of these was early block removal and conversion to oral analgesia. In the LIA and infusion group 14 patients had at least one catheter occlude with blood, three patients had significant leaking at catheter sites, and two patients had accidental dislodgment of one of the catheters.

Chapter 7

7 Discussion

The purpose of this randomized control trial was to assess whether periarticular infiltration and infusion has a comparable time-to-discharge, analgesic quality, and complication rate to motor-sparing nerve blocks (MSNB) in patients who have undergone primary total knee arthroplasty. Interim analysis demonstrated no significant difference between the two groups in terms of the primary outcome of time to discharge from hospital (p=0.47). The mean time to discharge for MSNB and periarticular infiltration and infusion was 2.57 days (SD ± 1.0) and 2.5 days (SD ± 1.25) respectively. Current studies comparing continuous peripheral nerve blocks with intra-articular infusion are limited, but the literature supports this finding. Beausang et al. randomized 96 patients to two study groups, continuous adductor canal block (n=50) and intraarticular catheter infusion (N=46) [134]. They failed to demonstrate any significant difference between groups for length of stay in hospital (mean: 1.8 days for both groups). In a meta-analysis of 10 studies involving intra-articular catheters, Sun et al. found no statistical difference in the length of stay length of stay compared to placebo [81].

Regarding our secondary outcome measures, there were no overall significant differences in visual analogue scale (VAS) pain scores at rest or with activity. Similar to our previous study [12], MSNB provided a significant decrease in early pain scores. MSNB provided superior analgesia at 6-hours post-op during rest and activity as well as the afternoon of post-op day one during activity. On the morning of post-op day 2, there was a significant difference in pain scores during activity that in contrast favored periarticular infiltration and infusion. Peripheral nerve block studies are notoriously difficult to compare, as their results rely heavily on a number of variables including insertional technique, block location, anaesthetic drug choice, concentration and infusion rate, as well as analgesic adjuncts [81,93]. Despite this, Beausang et al. found a similar result in that their adductor canal block group had significantly lower pain scores (3.60 ± 2.2 vs 4.38 ± 2.4, p= 0.02) early on prior to activity (physiotherapy) compared to continuous intraarticular infusion. Following the first data collection point, there were no

statistically significant differences in pain scores during and after activity [134]. In our previous study, MSNB also had statistically significant lower pain scores early on at 2- and 4-hours post-op with activity, and 2 hours post-op at rest [12].

The MSNB in our study is a modification of a standard adductor canal block to provide more posterior and lateral knee anaesthetic coverage as the knee is innervated by both the lumbar plexus (femoral and obturator nerves anterolaterally) and sacral plexus (sciatic nerve posteriorly) [22,135]. Adductor canal blocks have shown to be a reliable method of analgesia following total knee arthroplasty and provide the option of an indwelling catheter to prolong the block effect and decrease narcotic consumption [24,80,90,136,137]. Additionally, they have less risk of inhibiting quadriceps motor function and promote early ambulation in comparison to other more proximal regional methods such as epidural catheters and femoral nerve blocks [15,90,93,118]. With MSNB, placement of a perineural indwelling catheter provides the option to prolong the anaesthetic effect of the block through bolus or continuous dosing of local anaesthetic [80]. A substantial amount of evidence highlighting the potential benefits of continuous blocks exists, but few studies have compared single-injection adductor canal blocks versus a continuous technique directly.

Shah et al. performed a randomized control trial comparing single-injection versus continuous adductor canal blocks analgesic efficacy, early patient ambulation and functional recovery, as well as opioid consumption [135]. They found that the continuous group had statistically significant lower VAS pain scores at 4, 8 ,12, and 24 hours post op ($p<0.001$). There was also a significant difference in pain scores favoring the continuous block group at rest and activity on post-op day 1 and 2 ($p<0.001$). Two patients in the single-injection group required rescue opioid analgesia and none in the continuous group, which was consistent with other studies [92]. The results supported the notion that continuous infusion extended the effect of peripheral analgesia compared to a single- injection technique.

One would expect this outcome, as intuitively, having the ability to deliver more anaesthetic over time should yield a longer duration of analgesia. However, the results

comparing single-shot and continuous adductor canal blocks have been inconsistent. Zhang et al. performed a randomized, placebo-controlled trial comparing single-shot adductor canal block, continuous adductor canal block and a saline control group [120]. The primary outcome was visual analogue scale for pain during activity. When comparing the two adductor canal block groups, single- injection versus continuous, they found no differences in any outcome measures except procedural time (single-injection; 4 ± 1.4 minutes versus continuous; 20 ± 5.0 minutes) and complications. The continuous group had a vascular injury at the time of catheter insertion and one catheter accidentally dislodged from its insertion site. Considering the similar outcome measures, extra time involved to place the catheter, catheter cost, as well as increased risk of complications in the continuous group, they recommended using a single-injection technique for adductor canal blockade [120].

Bingham et al. performed a systematic review and meta-analysis of randomized controlled trials comparing single-injection to continuous peripheral nerve block techniques. They extracted data from 21 trials concerning pain scores, narcotic consumption, satisfaction and adverse effects. What was found was continuous peripheral blocks provided a significant decrease in pain scores on post-operative day zero (day of surgery) ($p=0.005$), one ($p<0.001$) and two ($p<0.001$). Patients who had a continuous block had significantly decreased narcotic intake and nausea symptoms and had higher overall patient satisfaction scores [92].

Though continuous techniques possess these appealing qualities, there are still several factors that inhibit their wide-spread implementation. Nerve blocks are carried out prior to surgery and require resources such as regional block specialists, dedicated space, and ultrasound that add to the overall treatment cost. It isn't without its risks either, with procedure specific complications including nerve injury, dense motor blockade, and catheter site complications [89,90,93].

Peripheral nerve blocks target a specific nerve branch proximally to anaesthetise its sensory distribution distally, while periarticular infiltration works by essentially flooding the tissue with anaesthetic and inhibiting the nerve fibres surrounding the surgical site.

Periarticular infiltration is an easy, safe, and effective analgesic modality for the management of post-op pain following TKA [17,103]. It possesses several similar qualities to MSNB such as maintenance of quadriceps function, promotion of early mobilization, and reduces opioid consumption without the additional resources and cost associated with MSNB and other peripheral blocks [12,17]. The issue that arises with periarticular infiltration is the reduced duration of analgesia, as a one-time dose of anaesthetic is delivered at the end of the surgical procedure [81,138]. In our previous study, Sogbien et al. demonstrated that a single-injection technique with MSNB provided significantly longer duration of analgesic effect, with a mean difference of 8.8 hours (95% CI= 3.98-13.62 hours, $p<0.01$) compared to periarticular infiltration [12]. Previous studies have found the duration of analgesic effect for periarticular infiltration to be variable and range anywhere from 8 to 48 hours [81]. Though effective, this method does not lend itself to easily be transitioned to a continuous regional technique as anaesthetic distribution needs to be diffuse to be effective. Several studies have explored the idea, utilizing a variety of anaesthetic drug combinations, infusion rates, and procedure techniques with variable results [81,125].

Ali et al. conducted a randomized control trial comparing intraarticular catheters in 200 patients undergoing total knee arthroplasty [110]. Ropivacaine was infused intraarticularly in the experimental group, while saline was used in the control group. Intra-operatively, both groups received periarticular infiltration with a drug cocktail of ropivacaine, ketorolac and epinephrine. Though not specifically stated in their paper, they were comparing a single dose infiltration technique with a continuous intra-articular infusion. Their primary outcome measure was VAS score for pain. The results of their study yielded that continuous intraarticular infusion only provided a statistically significant decrease in pain scores on post-op day one (12pm; $p=0.02$, 8pm $p=0.03$). Thus, continuous infusion did not extend the duration of analgesia as significantly as they had hypothesized [110].

Sun et al. performed a meta-analysis of 10 clinical trials utilizing intra-articular infusion catheters versus placebo in 735 patients [81]. Outcomes that were assessed were VAS scores a rest and activity at 24, 48, and 72 hours post-op, duration of surgery, length of

stay in hospital, and complications. Their resulted revealed that continuous intra-articular infusion provided statistically significant decrease in VAS pain scores at 24 hours during rest ($p<0.01$) and activity ($p<0.01$) and with activity at 48 hours ($p<0.01$). There was no difference between groups in regard to pain at rest at 48 hours as well as during rest and activity at 72 hours. The duration of surgery and the length of stay in hospital was also similar between groups.

Similar to adductor canal blocks, high quality randomized controlled trials directly comparing single-dose periarticular infiltration to continuous intraarticular are scarce. Zhang et al. randomized 80 patients to three different treatment groups, single-dose periarticular infiltration, continuous intra-articular infusion, and saline control group [138]. The primary outcome was VAS pain scores over 48 hours post-op. The analysis revealed that VAS scores were lower in the continuous infusion group compared to the single-dose infiltration group and were statistically significant at rest ($p<0.05$) from 8 to 48 hours post-op and during activity ($p<0.05$) from 16 to 48 hours post-op. Morphine consumption was significantly higher in the single-dose infiltration group ($p<0.05$). Maximum knee flexion at 7-and 90-days post-op was significantly increased in the continuous infusion group as well ($p<0.05$) [138].

Narcotic consumption was not significantly different between our experimental and control groups at any of the post-operative inpatient time points ($p= 0.59$). Periarticular infiltration and infusion consistently required more narcotic rescue analgesia compared to MSNB, but it was not significant (Table. 3). Our previous single- dose study demonstrated no significant difference in opioid consumption as well, but narcotic intake was nearly the same at all time points between groups [12]. Our results reflect those found by Beausang et al. [134]. When comparing adductor canal blocks to Intra-articular infusion, they found opioid consumption in morphine equivalents was not statistically significant at 24 ($p=0.057$) and 48 hours ($p=0.106$) post-op between groups. Similar to our study, they also observed that the total opioid consumption in the adductor canal block group was less than that of the intra-articular infusion group [134].

Nausea is a common side effect as a result of narcotic use and was quantitatively assessed using a 0-4 numeric scale (0=none, 1=mild, 2=moderate, 3=severe, 4= extreme) [75]. There was not a significant overall difference in nausea scores during the 6-day assessment period (p=0.21) similar to our previous study [12]. Previous studies have demonstrated that continuous analgesic methods may decrease nausea symptoms compared to single-shot techniques or placebo [80,81,90,138]. This may be due to the prolonged analgesic quality of the continuous blocks and results in less narcotic consumption [75].

Respiratory depression is a risk with large quantities of narcotics and so patient vitals were collected at each post-operative timepoint to ensure there were no significant respiratory side effects went unobserved [75]. There were no statistically significant differences in respiratory rate (p=0.54) and oxygen saturation (p=0.67) between groups during the inpatient stay.

Post-operative function was evaluated by assessing ability to perform physiotherapy at each time point as well as range of motion achieved. There were no significant differences between groups in ability to perform physiotherapy (p=0.49) as well as no differences in first flexion angle achieved (p=0.23) and best flexion angle achieved (p=0.15) while in hospital. Again, this was similar to what Sogbein et al. observed when no significant differences were found in patient's eligibility to perform physiotherapy or in time and length of first mobilization [12]. When assessing range of movement between groups, Beausang et al. also demonstrated no difference in active range of movement between groups at any of their assessment time points [134].

Regarding our patient reported functional outcome scores, there were no significant differences in the pre-operative and 3-month SF-12, WOMAC, or KSS outcome scores. This is consistent with our previous study and as well as the results published by Beausang et al. [12134]. Interestingly, there was a significant difference in the KSS expectations section of the questionnaire at the 6-week post-operative mark favoring the MSNB group, but is unlikely to be clinically relevant and was balanced by 3-months post-op. Our results demonstrated an improvement from pre-op scores for pain,

stiffness, mental and physical health, and function at the 3-month mark across both groups and was not significantly different between groups (Table 5, Table 6, Table 7).

The heterogeneity that is present across continuous peripheral nerve block and infusion studies inevitably makes it challenging to make generalizations on complication rates associated with these procedures, but there are some consistencies in the literature.

Largely, the risk of quadriceps weakness in adductor canal blocks is less compared to that of other regional techniques, though it still can occur [139]. In our study, one MSNB patient and one LIA and infusion patient suffered a delay in discharge of 2 and 4 days respectively due to quadriceps weakness. One patient in each group also suffered a transient foot-drop that resulted in a 1-day delay in discharge each. Though we could not find dense motor blockade as a previously described complication of periarticular infiltration, we suspect it occurred due to inability to direct infusion flow through the catheters and enough volume collected anteriorly and posteriorly to cause the adverse effect. All four patients suffered only transient loss of function and were discharged once their motor control returned.

The major concern with periarticular infusion catheters is the theoretical increased risk of prosthetic joint infection. Several studies have reported conflicting results. A meta-analysis of seven studies (579 patients) utilizing continuous intraarticular catheter infusions found there to be a significant increase in the rate of infection (relative risk [RR] 3.16, 95% CI 1.18-8.50, p=0.02) when compared to placebo [81]. These studies had small sample sizes though and only three of the seven reported infection occurring in the catheter group. A second metanalysis by Zhang et al. re-analyzed 6 of the 7 studies in the previous analysis and reiterated these results, finding a statistically significant difference in infection risk with intra-articular catheters (relative risk [RR} 3.45, 95% CI 1.16-10.33, p= 0.03) [125]. Of the 7 studies included across both meta-analyses, only one study was found to have a significant difference between groups in regard to infection. Ali et al. reported a significant difference (p=0.02) between groups at 3-month post-op, with 11 cases of infection in their intervention group (ropivacaine) and two cases in their control group (saline). Six of these cases were deep infections (five from the

intervention group) and all required surgical intervention. It should be noted though that their control group also had an intra-articular catheter in situ infusing saline. The risk of external contamination was still present, and thus they weren't able to fully explain why such a significant increase in infection occurred in their intervention group.

In contrast, during our assessment period there were no infections within the three months following surgery in either group. One LIA and infusion patient developed prolonged drainage from the site of the posterior catheter during the first two weeks post-op but did not require intervention. Similarly, Zhang et al reported no infections at 3 months post-operatively in either of their intervention groups [138]. Ham et al performed a large retrospective-analysis of 1915 patients at a single center to determine the rate of deep infection in patients who had received an intraarticular catheter. There was no statistically significant difference (in the deep infection rate, with the rate in intra-articular catheters being 0.53% as opposed to 0.77% in patients who did not receive a catheter [140]. Other randomized controlled trials have reiterated these results, finding no statistically significant difference in infection rate with intra-articular catheters [107,109]. Interestingly, local anaesthetics have demonstrated antimicrobial effects that may help counteract the increased risk of contamination through the intra-articular catheter [141].

Deep prosthetic joint Infection is a potentially serious complication that is unique to intraarticular catheters. Due to the relatively short follow-up period and small sample sizes in our own study as well as in the current prospective literature, further investigation is needed to define the true risk of Infection [81].

Another concern involving continuous infusions is the risk of local anaesthetic systemic toxicity. Symptoms of toxicity include circumoral numbness, metallic taste, pruritis, to more severe complications such as cardiac arrhythmias, cardiac arrest, seizures, respiratory arrest, and coma [89,93]. One patient in the LIA and infusion group suffered from local anaesthetic toxicity that was managed through block cessation and supportive treatment. Due to the heterogeneity in peripheral anaesthetic drug types, concentrations and infusion rates, no optimal infusion protocol has been identified [81,90]. Fortunately, anaesthetic toxicity is rare [80]. Sites et al. performed a retrospective review

of 12,668 patient who received ultra-sound guided nerve blocks and found the rar e to be 1.8 per 1000 blocks performed (CI 95%, 1.1-2.7) [94]. Several prospective randomized control trials assessing both perineural catheters as well as intra-articular catheters have also found this to be true, reporting no cases of local anaesthetic systemic toxicity in research subjects. [107,134,135]. Bleckner et al. investigated ropivacaine serum levels in trauma patients who received long-term peripheral anaesthetic infusions at high doses [142]. The median duration of perineural catheter infusion was 7 days (range: 2-23 days) with a median dose of 3722mg (range: 1146mg - 22,320mg). Despite the large doses incurred by some patients, ropivacaine serum free concentrations remained below toxic levels in all patients throughout the study and demonstrated a favorable safety profile for these analgesic techniques [142].

A number of mild adverse events occurred during the study period that have been previously described as potential problems with both intra-articular catheters as well as continuous nerve blocks.[80,81,89,93]. These include catheter occlusion, leakage, and dislodgement. In our trial, catheter occlusions were documented when failure to establish patency with a saline flush occurred. There was one case of catheter occlusion in MSNB group, where in periarticular infiltration and infusion group, 14 patients had at least one catheter occlude with blood. The reason for such a significant difference was not unexpected, as there are three points of possible occlusion in the LIA and infusion group and no control over the direction of infusion flow as it travels in the path of least resistance. The haemarthrosis that forms following surgery also predisposes the intraarticular catheter to occlusion. This may have affected the early analgesic quality resulting in a significant difference in early rest and activity visual analogue scores. One MSNB patient's catheter and two LIA and infusion catheters were accidentally dislodged from the entry sites during physiotherapy. There was one case of significant catheter site leakage in the MSNB group and three in the LIA and infusion group. The management for each of these was early block removal and conversion to oral analgesia. A complication described in the literature is retained portions of the indwelling catheter [134]. No cases of catheter retention occurred throughout the study period.

7.1 Study strengths

The strengths of our study begin with our conservative patient eligibility criteria to allow for as much internal and external validity in our results as possible. We strived to have the study sample represent the real-world population as best as possible while trying to remove some confounding variables such as pre-operative narcotic use and chronic pain. Our study utilized randomization to reduce our risk of selection bias, as well as control for unknown confounders. We used a single investigator to collect data at various time points rather than multiple inpatient care providers to increase the reliability of our data. Our experimental group utilized a unique three catheter arrangement not previously described in the literature in an effort to provide a more diffuse analgesic coverage comparable to MSNB. Few studies exist comparing continuous wound infusions with other peripheral nerve blocks, and we aimed to contribute to the current literature by comparing these two different regional anaesthetic approaches.

7.2 Study Limitations

This randomized-control study has a number of limitations that were discovered throughout the trial. The first limitation is the incomplete data and quoted results from the preliminary analysis. The reasons for this are that enrollment was not completed at the time of analysis, with 16 patients still required to reach study power, as well as the unfortunate timing of a nationwide shortage of ropivacaine that placed the study on a long hiatus. Thus, definitive conclusions on the primary outcome cannot be made from the data. The study was powered to find statistically significant differences in time to discharge from hospital. None of the secondary outcomes were factored into the power analysis and thus no definitive conclusions of the secondary outcomes can be made from the data upon completion. Another limitation is the small sample size, which lends itself to more variability and the chance of the study sample not being truly representative of the population.

Though the study was randomized using blocked random number sequence generation, there was a risk of selection bias occurring due to method of allocation concealment. Random number sequence generation was performed by an independent party, but envelop concealment was utilized for group allocation with a small blocking group of five, opening up the possibility the investigator could anticipate assignments.

The lack of blinding in our study patients, providers, assessors and analyzers puts the study at risk for potential biases. There was a risk of response bias due to patients having the knowledge they are in the control or experimental group and falsely inflate or deflate their responses for a number of reasons including their previous experience, their personality, and their relationship with the assessor. There was also a significant risk of performance and detection bias due to the lack of blinding of participants, personnel, and assessors as the outcome of pain is highly likely to be influenced by knowledge of the treatment group. Expectation bias is also a possibility with patients expecting have a greater improvement in pain with the use an experimental treatment (periarticular infiltration and infusion) versus standard methods. This increases the experimental treatment response and decreases the signal detection between the two treatment groups.

Though both treatments continuously delivered anaesthetic, there were some unavoidable inequalities. In the MSNB group, there is less procedural variability as a single catheter is accurately placed under ultra-sound guidance, decreasing the likelihood of block failure. In periarticular infiltration and infusion, there are three catheters, with one being placed posteriorly without ultrasound guidance. These catheters had less precise placement in comparison to the MSNB and direction of infusion flow was not controllable, taking the path of least resistance between the three catheters. Though there was not an overall significant difference in pain scores in the interim analysis, these discrepancies could add to the explanation as to why MSNB demonstrated superior early analgesia at rest and with activity and are a limitation.

We did not collect blood samples to assess for serum ropivacaine levels and is a potential limitation in our study. Though we only had one documented symptomatic

event of anaesthetic toxicity, we are not able to comment on if other patient's blood levels reached toxicity and were asymptomatic with the high infusion rate (8ml/hr) and volume we were using.

Another limitation of our study involves the data collection time points. Patients had variable operative times on the day of surgery, and thus having fixed data collection points (9am and 2pm on each post-operative day) meant some patients were assessed earlier or later depending on their time of surgery. This could affect secondary outcomes measures including pain scores, ability to perform physiotherapy, and narcotic consumption between data collection points.

Chapter 8

8 Conclusion

8.1 Clinical Relevance

The goal of our randomized control trial was to assess whether periarticular infiltration and infusion has comparable clinical and functional outcomes to that of motor-sparing nerve blocks in patients who have undergone primary total knee arthroplasty. The use of motor sparing nerve blocks for analgesia following TKA has been supported through our previous work as well as the existing literature. Though it is an effective treatment, it is not a feasible option for the majority of orthopaedic surgeons that perform knee replacements, especially in community settings. The additional skills and cost required to provide nerve blocks consistently to patients make them difficult to implement in a resource constrained health care system. It is our duty as a larger tertiary center to explore continuous regional anaesthetic options that are comparable to our standard of care and can realistically be adopted by our colleagues who don't have access to such analgesic options. A practical anaesthetic technique needs to be relatively inexpensive, encourage narcotic stewardship, promotes early ambulation so as not to delay discharge, and not have a significant increase in complications such as infection, dense motor blockade, or a high rate of failure. Our interim analysis supports this effort thus far by yielding non- significant results between our experimental and control groups for our primary outcome of time-to-discharge, pain scores at rest and activity, narcotic consumption, as well as patient reported functional outcomes.

8.2 Future direction

Our future direction for the study is to finish enrollment and the trial and continue to explore the application of periarticular infiltration and infusion in patients undergoing primary total knee arthroplasty. We plan to perform a retrospective review of study patients to assess for late complications such as prosthetic joint infection that could be associated with periarticular infiltration and infusion and determine if it is a significant

risk. Cost effectiveness analysis is also a future plan, as we must provide evidence that periarticular infiltration and infusion doesn't significantly add to the overall cost of the procedure, while being a less expensive modality than motor-sparing nerve block. We will then explore the interest in peripheral centers for such a treatment option and assist in its implementation into their post-operative care plans. A potential future study for periarticular infiltration and infusion will be its roll in out-patient analgesia for same-day or fast-tracked discharge following total knee arthroplasty by allowing patients to be ambulatory with their regional block.

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9 Appendix A: Ethics Approval

LAWSON FINAL APPROVAL NOTICE

LAWSON APPROVAL NUMBER: R-12-498

PROJECT TITLE: Outcomes after Total Knee Joint Arthroplasty: A comparitive study using 3 different analgesic techniques.

PRINCIPAL INVESTIGATOR: Dr. James Howard

LAWSON APPROVAL DATE: 17/07/2017

ReDA ID: 1047

Overall Study Status: Active

Please be advised that the above project was reviewed by Lawson Administration and the project:

Please provide your Lawson Approval Number (R#) to the appropriate contact(s) in supporting departments (eg. Lab Services, Diagnostic Imaging, etc.) to inform them that your study is starting. The Lawson Approval Number must be provided each time services are requested.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

Western Research

Date: 17 September 2018

To: Dr. James Howard

Project ID: 101754

Study Title: Outcomes after Total Knee Joint Arthroplasty : A comparative study using 3 different analgesic techniques (REB #18448)

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 02/Oct2018

Date Approval Issued: 17/Sep/2018

REB Approval Expiry Date: 04/Oct/2019

Dear Dr. James Howard,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Daniel Wyzynski, Research Ethics Coordinator, on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western Research

Date: 5 January 2018

To: Dr. James Howard

Project ID: 101754

Study Title: Outcomes after Total Knee Joint Arthroplasty : A comparative study using 3 different analgesic techniques (REB #18448)

Application Type: HSREB Amendment Form

Review Type: Delegated

Full Board Reporting Date: January 23, 2018

Date Approval Issued: 05/Jan/2018

REB Approval Expiry Date: 04/Oct/2018

Dear Dr. James Howard ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date
Block Room Instructions 28-Nov-2017	Other Materials	28/Nov/2017
Physician Reference Sheet 21-Nov-2017 CLEAN	Other Materials	21/Nov/2017
Protocol 21-Nov-2017 CLEAN	Protocol	21/Nov/2017

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Karen Gopaul, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western Research

Date: 13 June 2018

To: Dr. James Howard

Project ID: 101754

Study Title: Outcomes after Total Knee Joint Arthroplasty : A comparative study using 3 different analgesic techniques (REB #18448)

Reference Number/ID: N/A

Application Type: HSREB Amendment Form

Review Type: Delegated

Full Board Reporting Date: June 19, 2018

Date Approval Issued: 13/Jun/2018

REB Approval Expiry Date: 04/Oct/2018

Dear Dr. James Howard ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date
Letter of information and consent form 09-May-2018 CLEAN	Consent Form	09/May/2018
Protocol 10-Apr-2018 CLEAN	Protocol	10/Apr/2018

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Karen Gopaul, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

10 Appendix B: Letter of Information and Consent

Letter of Information and Consent Form

Outcomes after Total Knee Joint Arthroplasty: A comparative study using different analgesic techniques

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Principal Investigator
Dr. James Howard

Research Assistant
Dr. James Allen

Co-Investigators
Dr. Brent Lanting
Dr. Edward Vasarhelyi
Dr. Peter Mack
Dr. Sugantha Ganapathy
Dr. Mahesh Nagappa
Dr. Deepti Vissa

You are being invited to voluntarily participate in a research study conducted by the Department of Orthopedic Surgery and Departments of Anesthesiology and Perioperative Medicine at the University of Western Ontario. As a patient scheduled to have a Total Knee Replacement (TKR), we invite you to consider taking part in this research study. This letter of information describes the research study and your role as a participant. Please read this letter of information carefully. Do not hesitate to ask anything about the information provided. Your surgeon, anesthesiologist or the study coordinator will describe the study and answer your questions. Your decision is completely voluntary and will not affect your medical care if you choose not to participate. You may take as much time as you need to decide whether to participate and can discuss participation with your friends, family, family doctor, etc.

WHY ARE WE DOING THIS STUDY?

The operation you will be having (Total Knee Replacement, shortened to TKR) is a very common one. However without proper treatment the first 2 to 3 days after the operation can be very painful. There are several different options for providing pain relief while you are in hospital after a TKR.

The current methods to control pain following knee surgery in our hospital include oral medications combined with either nerve block or wound infiltration with freezing agent. A nerve block is an anesthetic injection (freezing) targeted toward a certain nerve or group of nerves to treat pain. The purpose of the injection is to "turn off" a pain signal coming from a specific location in the body (in your case the knee). Ultrasound is used to help the doctor place the needle in exactly the right location so that you can receive maximum benefit from the injection. Sometimes, these nerve blocks can make your leg weak with a potential for you to fall down. Performing these blocks in the mid-thigh level can minimize leg weakness while providing good quality pain relief. Usually a tiny tube (block catheter) is placed close to the nerve carrying sensation from the knee joint which is connected to a pump delivering freezing around the same nerve. These nerve blocks are continued after surgery so that the surgical wound is frozen as long as the blocks are in place. Alternately, the surgeon may insert tiny tubes around the joint at the end of surgery to deliver freezing around the joint (called wound infiltration). These tiny

tubes are connected to a balloon pump delivering freezing directly into the wound. Along with the nerve blocks or freezing around the joint, you are provided with oral medications for pain relief. The pain management techniques performed as a part of the study are commonly offered to all patients undergoing TKR.

With all these measures, a healthy individual without any major medical or surgical problems should be able to do physiotherapy exercises with well controlled pain following the surgery. If you can achieve the rehabilitation goals (do the physiotherapy exercises) within the first day following surgery, you may be suitable to be sent home while continuing the same pain management measures.

The aim of this study is to determine the effectiveness and safety of the different pain-relieving techniques.

WHAT DOES THE STUDY INVOLVE?

If you are eligible and agree to participate in the study, you will be randomized, like the flip of a coin, to one of the two pain treatment groups during your visit to the preadmission clinic. To provide anesthesia during the operation you will receive a spinal anesthetic. This will numb the entire lower half of your body for about 4 hours. The group you are randomized to will determine the method of postoperative pain relief. Your surgical procedure will not be changed as a result of your participation in the study.

Group 1: *Patients in this group will receive what are known as 'motor sparing nerve blocks' before the operation*. This involves numbing the 2 nerves, which supply the bulk of the sensation to the knee. A small plastic tube will be inserted close to the nerves supplying the knee joint combined with injecting freezing behind the knee using an ultrasound. The anesthetic doctor will explain the details of the procedure to you. Dilute local anesthetic (freezing) is delivered via these tubes until discharge, keeping the operated knee numb during that period.

Group 2: *This group will receive freezing solution injected into the wound at the end of surgery by the surgeon*. The surgeon will leave 3 very fine tubes inside the wound just before it is closed. During the two days after the operation very small amounts of freezing solution will be delivered through these tubes into the wound, in order to numb the knee.

You will receive multiple oral pain killers called multimodal analgesia starting in the preoperative period as needed according to the standard of care for University Hospital. This will allow your pain to be managed better.

Following the operation you will be followed up closely until you are discharged from hospital. You will be assessed on a regular basis for any pain, feelings of nausea or sedation, and how you are progressing with your physiotherapy. All participants will be assessed for discharge criteria by the research staff 6 hours after surgery and twice daily until discharge. If you meet the discharge criteria and maintain it at the next evaluation, your indwelling anaesthetic tubes will be removed, and you will be discharged home with the care orders normally given to all patients.

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Participant's Initials

The discharge criteria include satisfaction of the first four of the five criteria:

1. You should be able to take care of personal care, get in and out of bed, into and up from a chair, on and off a toilet and to walk with proper walking aids 70 m without time limit; ability to do five steps.
2. Free of medical or surgical complications including urinary catheterization or need for blood transfusion
3. Acceptable pain relief (NRS $\leq$ 5/10) without any need for intravenous analgesics.
4. No nausea/ vomiting; generalized weakness or dizziness.
5. Knee flexion of 90^0 is optional but preferred.

A pain diary will be given to you before you are discharged to record your pain, the degree of knee movement, the success of physiotherapy, any feelings of nausea or sedation, post-operative complications, and the amount of pain killers that you have taken twice daily. You will be asked to complete this diary for 4 days after you are discharged from hospital. You will be educated on how to complete your post-operative pain diary before you leave the hospital. Research staff will call you at home on days 1 and 4 after you have been discharged from hospital to answer any questions you may have about the pain diary. This diary will be returned to the research staff at your next appointment with your surgeon (at 2 weeks after surgery).

Reasons for delay in discharge will be collected. The research team will obtain data regarding any complications that you may develop while you are in the hospital from the hospital chart, and any that develop after discharge by talking to you and your surgeon at each of your standard follow-up appointments in clinic. Any complication that you may develop will be managed as per the standard practice at London Health Sciences Centre.

You will be asked to complete 3 questionnaires (SF-12, WOMAC and Knee Society Score) at your preadmission appointment before surgery and at 6 weeks and 3 months after surgery. These questionnaires ask about your general health, pain and function. At your 2 week visit to clinic, the research staff will measure the range of motion of your knee and ask about your pain. There are no extra visits required as part of this study. Follow-up appointments at 2 weeks, 6 weeks and 3 months are all standard of care for the surgeons involved in this study.

RISKS

Regional nerve blocks have been shown to be a very safe alternative to general anesthesia. However, just as general anesthesia carries risks, regional anesthesia entails certain risks too. Serious risks are very rare, but they are of a different nature to those of general anesthesia and the risks are detailed below. The numbers below indicate the risk of each problem. For example 1/10,000 means on average 1 in every 10,000 patients undergoing a nerve block will suffer that problem.

1. Failed block: The block may provide inadequate pain relief. This occurs in 5/100 to 10/100 of patients. If this occurs, alternative oral or intravenous medications such as morphine or dilaudid will be used to make you comfortable.
2. Risk of suffering some degree of bruising from the needle injection site – 1/10 to 1/100.

_____
Participant's Initials

3. Temporary nerve irritation leading to an area of numbness or tingling persisting for up to a week – 1/100
4. Risk of suffering a temporary seizure due to the local anesthetic being too rapidly absorbed – very rare. 1/10,000 to 1/100,000.
5. Risk of suffering longer-term nerve damage lasting several months – very rare. 1/5000 to 1/10,000.
6. Risk of suffering permanent nerve damage – very rare – 1/100,000,000.

Side effects from the sedation include short-term (a few minutes to a few hours) drowsiness, forgetfulness and sometimes minor temporary itching.

Wound infiltration and infusion of local anesthetic may be associated rarely with toxicity from absorbed local anesthetic, nerve injury and infection. The exact frequency of these problems is currently unknown.

A member of the research team will explain all the details during your visit to the preadmission clinic.

EXPECTED DURATION OF THE STUDY AND NUMBER OF SUBJECTS EXPECTED TO PARTICIPATE

There will be about 70 people in this study, which will be conducted at University Hospital, London. The study is expected to run for one year; however your participation is expected to last 3 months (from surgery until your 3 month follow-up appointment).

STUDY RESTRICTIONS/PARTICIPANT RESPONSIBILITIES

As a participant in a research study, you have certain responsibilities.Your responsibilities are to:

1. Follow procedures as instructed
2. If possible, answer the study related questions asked by the research team
3. Report all changes in your physical or mental condition during the course of the study, whether or not you feel they are related to the study procedures

The study doctor has the right to stop your participation in the study at any time, with or without your consent, if he or she feels that this is in your best interest.

The study or part of the study may be stopped at any time at the discretion of your study doctor, or the University of Western Ontario Health Sciences Research Ethics Board.

Tell a study doctor immediately if you have a side effect from the treatment.

All female patients in the childbearing age group not practicing acceptable methods of contraception will have a urine pregnancy test done on the morning of surgery. Subjects who test positive for the pregnancy test will not be able to participate in the study

_____
Participant's Initials

London Health Sciences Centre

Schulich MEDICINE & DENTISTRY

BENEFITS

Participation in this study may or may not be of a direct benefit to you. It is possible your pain relief may be better as you will be very closely monitored while you are in hospital.

ALTERNATIVES TO STUDY PARTICIPATION

If you decide not to participate in this study it will NOT prejudice your care. After discussion with your anesthesiologist you will receive the most appropriate anesthetic which will suit you the best for the procedure you are having done.

VOLUNTARY PARTICIPATION

Your participation in this study is completely voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with NO effect on your future care. You do not waive any legal rights by signing the consent form.

PRIVACY AND CONFIDENTIALITY

All records compiled during this study in which you are identified will be kept confidential, and will not be disclosed outside the research group except as required by law and as described below.

Tests and procedures done solely for this research study may be placed in your medical record to indicate your participation in this study. Upon completion of the study, you may have access to the research information if contained in the medical record.

Representatives of the University of Western Ontario Health Sciences Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research. You do not waive any legal rights by signing the consent form. If you choose not to sign the consent form, you will not be included in this research study. You may choose to withdraw from the study even after consenting for the participation in the Study. If you choose not to sign the consent form, you will not be *included* in this research study.

RESEARCH RELATED INJURY

If physical injury occurs due to your involvement in this research, medical treatment will be available to you as per the standard care at our institution provided by OHIP. Compensation for lost wages and/or direct or indirect losses is not available.

COST/COMPENSATION

There will be no additional costs to you as a result of being in this study. You will not be compensated for participation in this study.

_____
Participant's Initials

London Health Sciences Centre

Schulich MEDICINE & DENTISTRY

CONTACT FOR QUESTIONS

Before you sign the consent form, you should ask questions about anything that you do not understand. The study staff will answer questions before, during, and after the study.

If you have questions about this study or how it is being run, you should contact Dr. James Howard, the principal investigator at [redacted] or the research assistant, Dr. James Allen at [redacted] at London Health Sciences Centre, University Hospital. If you have any questions about your rights as a research participant you may contact the Office of Human Research Ethics [redacted]ca.

In case of an emergency, please contact Dr. James Howard at 5 OR go to the nearest hospital emergency department.

_____
Participant's Initials

London Health Sciences Centre

Schulich MEDICINE & DENTISTRY

Consent Form

Outcomes after Total Knee Joint Arthroplasty: A comparative study using different analgesic techniques.

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction. I will receive a copy of the Letter of Information and this signed consent form.

Print participant's full name	Date
Participant's signature	
Name of person obtaining consent	Date
Signature of person obtaining consent	

_____
Participant's Initials

11 Appendix C: Image use consent

From: [redacted]
Subject: Re: Photius.com Feedback
Date: 19 March 2019 at 06:56
To: [redacted]

Hello James Allen,

Thank you for your inquiry,

You are welcome to use the text and images, and we request that you acknowledge the source as:

"Source: theodora.com/anatomy, used with permission", and in case of online publication, that you also place a link to the site:

"Source: theodora.com/anatomy, used with permission".

Regards,

Photius Coutsoukis

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> James Allen
>
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>
> r_Email_2:
>
> email_subject:
> Photius.com Feedback
>
> Message:
> Hello,
> My name is James and I am a orthopaedic resident and current master's student at the University of Western Ontario. I am currently writing my thesis titled "POST-OPERATIVE ANALGESIA FOLLOWING TOTAL KNEE ARTHROPLASTY: A RANDOMISED CONTROL TRIAL COMPARING REGIONAL TECHNIQUES" and was wondering if I could kindly request the use of your images as they are great Grey's illustrations. The list includes:
> Knee joint:
> Figure 345
> Fig. 346
> Fig. 347
>
> Thigh cutaneous distribution:
> Fig. 825
> Fig. 826
>
> Femur:
> fig 244
> fig 245
>
> Popliteal artery
> fig. 552
>
> Usage would be in the lit review section and would be full credited. I really appreciate your time and I look forward to hearing back from you.

From: Daryl Goldman
Subject: Re: Figure use for thesis
Date: 27 March 2019 at 10:15
To: James Aller

Hey sorry,

It is fine as long as you get permission from the publisher.

Thanks,
Daryl

On Wed, Mar 27, 2019 at 9:50 AM James Allen < wrote:

> Hi Dr. Goldman,
>
> Hope you are doing well. Any chance you have heard from your co-authors about the use of the image? I am terribly sorry for the repeated messages and I know how busy you are. I appreciate your time!
>
> Thanks,
>
> Dr. James H. Allen
>
> PGY1 Orthopaedic Surgery
>
> Western University

From: Daryl Goldman <>
Date: Thursday 21 March 2019 at 16:39
To: James Allen <>
Subject: Re: Figure use for thesis

Hi James!

Let me check with the other authors.

Thanks,

Daryl

On Thu, Mar 21, 2019 at 4:38 PM James Allen > wrote:

> Hello Dr. Goldman,
>
> My name is James Allen and I am an Orthopaedic Surgery resident at Western University, Ontario and a current Masters of Surgery student. I writing my thesis currently on the subject of post-op pain control following total knee arthroplasty. The title is “POST-OPERATIVE ANALGESIA FOLLOWING TOTAL KNEE ARTHROPLASTY: A RANDOMISED CONTROL TRIAL COMPARING REGIONAL TECHNIQUES”. I was wondering if it would be possible to get your approval for the use of a figure in a recent paper of yours, “Current Concepts and Future Directions of Minimally Invasive Treatment for Knee Pain”, specifically Figure 1 demonstrating the knee neuroanatomy as it is a fantastic image.
>
> Its use would be in the literature review section and would be listed with a proper citation.
>
> I appreciate the time and look forward to your reply.
>
> Thanks,
>
> James H. Allen
>
>

> it was originally intended is strictly prohibited. If you are not an intended recipient, please notify the sender immediately via a return email and destroy all copies of the original message. Thank you for your cooperation.

--

Best,

Daryl Goldman, MD
PGY1 - Department of General Surgery, Lenox Hill Hospital
Ema

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--

Best,

Daryl Goldman, MD
PGY1 - Department of General Surgery, Lenox Hill Hospital
Email:
Cell:

From: **Oliver Jone**
Subject: RE: New submission from Contact us
Date: 24 March 2019 at 07:38
To:

OJ

Dear James,

Thanks for getting in touch – you are more than welcome to use this image in your thesis as described in your email.

Best wishes,
Oliver

Dr Oliver Jones
Founder - The TeachMeSeries

From: TeachMeAnatomy
Sent: 21 March 2019 20:45
To: Oliver Jones
Subject: New submission from Contact us

New message from teachmeanatomy.info

Name
James
Email
Subject
Use of photo for thesis (TIME SENSITIVE)
Message
To Whom it may concern, My name is James Allen and I am a first year Orthopaedic Resident at UWO in Canada and a masters student. I am writing to you with a request for permission for the use of one of your photos, "Fig 1.0 – Cross-section of the thigh, showing the borders of the adductor canal. Note: the adductor magnus is not visible in this illustration" on the adductor canal webpage. I am looking to use it in the literature review section of my thesis and it will be appropriately cited. Thanks -James

Do not reply to this message, use the email address provided to reply to user.

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Licensed Content Date	Dec 31, 2014
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Title of your thesis / dissertation	POST-OPERATIVE ANALGESIA FOLLOWING TOTAL KNEE ARTHROPLASTY: A RANDOMISED CONTROL TRIAL COMPARING REGIONAL TECHNIQUES
Expected completion date	Aug 2019
Estimated size (number of pages)	120
Requestor Location	
	Attn: Western University
Total	0.00 CAD
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Licensed Content Author	Daryl T. Goldman, Rachel Piechowiak, Daniel Nissman et al
Licensed Content Date	Jan 1, 2018
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Licensed Content Issue	9
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Format	print
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	1
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Circulation/distribution	<501
Author of this Springer Nature content	no
Title	POST-OPERATIVE ANALGESIA FOLLOWING TOTAL KNEE ARTHROPLASTY: A RANDOMISED CONTROL TRIAL COMPARING REGIONAL TECHNIQUES
Institution name	n/a
Expected presentation date	Aug 2019
Portions	From the following paper, "Current Concepts and Future Directions of Minimally Invasive Treatment for Knee Pain" I am hoping to use the image Fig. 1 in my thesis. Thank you
Requestor Location	
	Attn: Western University
Total	0.00 USD

James Hilliard Allen Curriculum Vitae

Educational Background

Orthopaedic Surgery Resident 2018-2023, Department of Orthopaedic Surgery, Schulich School of Medicine, Western University

MB, BCh BAO (NUI, RCSI), LRCP&SI, Royal College of Surgeons in Ireland- 2010- 2016

Six-Year Program. Graduated with Honours

Certifications and Assessments:

Advanced Trauma Life Support- June 2018

Advanced Cardiac Life Support and renewal of Basic Cardiac Life Support- June 2018-2020

Standard First Aid & CPR- Basic Cardiac Life Support (BCLS)- June 2018-2020

Research Experience:

Surgeon Scientist Program: Schulich School of Medicine and Dentistry- Western University - September 2017-August 2019

MSc Degree (candidate)

Thesis title: Outcomes after Total Knee Joint Arthroplasty: A comparative study using different analgesic techniques

Description:
- Prospective randomized control trial
- Assessing two possible local anesthetic modalities following unilateral Primary Total Knee Arthroplasty
- Two groups include the control group, Motor Sparing Nerve block, and the intervention group, Local Infiltration anaesthesia plus periarticular infusion.
- Collected data points include analgesic quality, side effects and complications, narcotic consumption, and functional outcomes preoperatively and postoperatively

Required Courses:
- Advanced Principles of Surgical Research
- Advanced Surgical Research Colloquium

- Advanced Statistics and Research Methods for Surgeons

Head Injury in Patients with Hip Fractures: A Retrospective Review

- Data collection and second author roles
- Assessing the indications and frequency of CT head scans in the hip fracture population
- Assessing the appropriateness of the Canadian CT Head Rules/ New Orleans Criteria in this population
- Poster presentation at the 2018 American Academy of Orthopaedic Surgeons and the 2018 Canadian Orthopaedic Association annual meetings
- High scoring poster award at the Canadian Orthopaedic Association annual meeting

Orthopaedic Research: Mount Sinai Hospital- University of Toronto- September 2016-December 2017

Revision Hip Arthroplasty long-term survivorship study using the Zimmer ZMR Modular Hip System

Description:

- Retrospectively reviewed 335 patients who received a Tapered or Porous ZMR femoral component between 1999 to 2006 at Mount Sinai Hospital
- Follow-up studies conducted to reassess the same patient groups from previous mid-term survivorship papers from Mount Sinai published in 2010
- Reviewed Tapered and Porous groups separately to assess follow-up and complications to determine rate of failure
- Patients were contacted if digital records were inadequate
- Harris Hip scores were obtained to determine post-operative functional outcomes
- Follow-up radiographs were classified for component osseous integration and proximal bone stock by fellowship trained arthroplasty surgeons
- Podium Presentation at the 2018 American Academy of Orthopaedic Surgeons and the 2018 Canadian Orthopaedic Association annual meetings

Professional Experience

Rural Orthopaedic Surgery: Cape Breton Regional Hospital- November 2016

Two-week elective with Dr. Kevin Orrell, former Canadian Orthopaedic Association President

Description:

- Operating Room privileges with hands-on participation in 15 cases
- Clinic privileges using clinical knowledge to develop management plans for various Orthopaedic conditions
- One-on-one teaching from consultant Orthopaedic surgeons
- Further Rural medicine experience and understanding of the Nova Scotia Healthcare System

Community Orthopaedic Surgery: Chatham-Kent Health Alliance- January 2016

Three-week elective with Dr. John Turnbull

Description:
- Operating Room privileges participating in approximately 30 cases
- Clinic privileges and further involvement as I was the only student
- One-on-one teaching from consultant Orthopaedic surgeons
- Full time on-call for the full elective period
- Further Rural medicine experience and understanding of the Ontario Health System

General & Orthopaedic Oncology Surgery: Dalhousie University- September 2015

Two-week elective in Halifax Infirmary with Dr. Michael Biddulph

Description:
- Clinical elective including direct patient contact in clinical settings (in and out-patients)
- Operating room privileges observing and participating in approximately 30 cases
- Attended all resident teaching sessions, on-call, and grand-rounds
- Attended weekend-call while at Halifax Infirmary assisting junior and senior residents
- Worked alongside final-year residents, fellows, and other visiting elective medical students in the clinics, operating room, and in-patient wards
- Further development of Orthopaedic history taking and physical exam skills as well as obtaining more knowledge in establishing working differential diagnoses
- Further knowledge into the potential treatment options of various Orthopaedic injuries, congenital skeletal defects, and reconstructive procedures
- Development of the communication skills required to work in a cohesive surgical team

Arthroplasty & Trauma Orthopaedic Surgery: Schulich School of Medicine and Dentistry- Western University - August 2015

Three-week elective with Dr. James Howard, participated in the operating rooms of Dr. Brent Lanting, Dr. David Sanders, as well as the out-patient clinics and operating rooms of Dr. Edward Vasarhelyi.

Description:
- Clinical elective including direct patient contact in clinical settings (in and out-patients)
- Operating room privileges observing and participating in approximately 30 cases
- Attended all resident teaching sessions, on-call and grand-rounds
- Worked alongside final-year residents, fellows, and other visiting elective medical students
- Further development of Orthopaedic history taking and physical exam skills as well as obtaining more knowledge in establishing working differential diagnoses.
- Further knowledge into the potential treatment options of various Orthopaedic injuries, congenital skeletal defects, and reconstructive procedures
- Development of the communication skills required to work in a cohesive surgical team

Orthopaedic Oncology Surgery: University of Toronto- July 2015

Two-week elective in Mount Sinai Hospital with Dr. Peter Ferguson

Description:
- Clinical elective including direct patient contact in clinical settings (in and out-patients)
- Operating room privileges observing and participating in approximately 20 cases
- Attended all resident teaching sessions, tumor board meetings with multi-disciplinary team, on-call, and grand-rounds
- Worked alongside final-year residents, fellows, and other visiting elective medical students in clinic and operating rooms
- Participated in the operating rooms and out-patient clinics of Dr. Jay Wunder extensively during the two-week elective period
- Further development of Orthopaedic history taking and physical exam skills as well as obtaining more knowledge in establishing working differential diagnoses
- Further knowledge into the potential treatment options of various Orthopaedic injuries, congenital skeletal defects, and reconstructive procedures
- Development of the communication skills required to work in a cohesive surgical team

Pediatric Orthopaedic Surgery: McMaster University- July 2015

Two-week elective in McMaster University Medical Centre with Dr. Paul Missiuna

Description:
- Clinical elective including direct patient contact in clinical settings (in and out-

patients)
- Operating room privileges observing and participating in approximately 15 cases
- Attended all resident teaching sessions, on-call, and grand-rounds
- Worked alongside final-year residents, fellows, and other visiting elective medical students
- Participated in the operating rooms and out-patient clinics of Dr. Devin Peterson, Dr. Jung Mah, Dr. Rick Ogilvie extensively as well as participated in the clinics of Dr. Bradley Petrisor, and Dr. Sarah Burrow
- Further development of Orthopaedic history taking and physical exam skills as well as obtaining more knowledge in establishing working differential diagnoses
- Further knowledge into the potential treatment options of various Orthopaedic injuries, congenital skeletal defects, and reconstructive procedures
- Development of the communication skills required to work in a cohesive surgical team

Community Orthopaedic Surgery: Schulich School of Medicine and Dentistry-Western University, SWOMEN program- June-July 2015

Two-week elective through the Southwestern Ontario Medical Education Network with Dr. John Turnbull

Description:
- Operating Room privileges participating in approximately 25 cases
- Clinic privileges and further involvement as I was the only student
- Further Rural medicine experience and understanding of the Ontario Health System
- Extensive involvement in the operating room with Dr. John Turnbull, Dr. Hans Hundt, Dr. Jonathan Stone, and Dr. Zaheer Kukkadi as surgical assist
- Further development of Orthopaedic history taking and physical exam skills as well as obtaining more knowledge in establishing working differential diagnoses
- Further knowledge into the potential treatment options of various Orthopaedic injuries, congenital skeletal defects, and reconstructive procedures
- Development of the communication skills required to work in a cohesive surgical team

Orthopaedic Research: Western University: January-March 2014

Six weeks in the Fowler Kennedy Clinic with Dr. Kevin Willits

Description:
- Completed clinically relevant retrospective review looking at bone healing with computed tomography following medial opening wedge high tibial osteotomy
- Attended clinics at Fowler Kennedy
- Attended operating room cases relevant to the research as well as supplemental operating room time for further experience and knowledge

Orthopaedic Surgery Observership: Chatham-Kent Health Alliance June–August 2013

Ten weeks of Orthopaedic Surgery observership in Chatham, Ontario under Dr. Hans Hundt.

Description:
- Participated in daily routines observing Dr. Hans Hundt and Dr. John Turnbull.
- Participated in surgical rounds for in-patients
- Took part in weekly clinics and ambulatory care
- Observed and assisted with over 140 Orthopaedic surgical cases ranging from total joint arthroplasty to arthroscopy
- Attended on-call with Dr. Hundt
- Gained knowledge of basic pathological, physiological, and natural disease history principles of common Orthopaedic conditions and injuries

Extracurricular Activities & Involvement

Peer-led Tutor: Royal College of Surgeons Ireland 2015-2016

Description:
- Tutorials in Orthopaedic Physical Examination.
- Small group teaching tutorials for students beginning their clinical learning.

President of the Royal College of Surgeons Orthopaedic Society: 2015-2016

Description: 400+ member society focused on increasing the interest and teaching the basic principles of Orthopaedic surgery.
- Further development of previous events such as Orthopaedic tool representative talks
- Development of events to engage students and peak interest in the field of Orthopaedic Surgery
- Organization of case presentations and Journal Clubs
- Provision of peer-led teaching tutorials on Orthopaedic Physical Examination
- Provided assistance to younger students with preparation for summer Orthopaedic electives.
- Organized and successfully completed an introduction to plaster casting event

Board Member Orthopaedic Society: Royal College of Surgeons 2014-2015

Description:

- Event coordinator responsible for planning and organization of educational and entertaining society events for members
- Provided students further knowledge into the profession of Orthopaedic Surgery
- Branding development and social-media management for the society