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Blood Conservation in Total Hip Arthroplasty: Interim Analysis of the Tranexamic Acid Comparison in Hip Replacement (TeACH-R) Trial

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Graduate Program in Surgery
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science
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INTERIM ANALYSIS OF THE TRANEXAMIC ACID COMPARISON IN HIP
REPLACEMENT (TeACH-R) TRIAL

Monograph Format

by

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Master of Science in Surgery

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Abstract

Intravenous tranexamic acid (TEA) is used in total hip arthroplasty (THA) to reduce blood loss. Concern of increased thromboembolic risk has prompted the search for treatment alternatives. The Tranexamic Acid Comparison in Hip Replacement (TeACH-R) trial is a prospective randomized controlled trial comparing the efficacy of intravenous and topical TEA in reducing perioperative blood loss. For interim data analysis, 52 of the planned 144 participants had completed the initial phase of the TeACH-R trial. No significant differences were identified between the intravenous and topical TEA treatment arms for delta-hemoglobin (ΔHgb; 34.81±13.78 vs. 35.65±15.54 mg/dL; p=0.840), calculated blood loss (1548±509 vs. 1521±693 mL; p=0.873), or length of stay (55.0±11.44 vs. 54.5±20.1 hours; p=0.912). No participant required a blood transfusion or had a thromboembolic event postoperatively. Promising initial results support the use of topical TEA in THA, although therapeutic decisions should be made only once all data has been analyzed.

Keywords

Acknowledgments

The fate of many a research study is never solely dependent on the efforts of one single person. It is the collective involvement of a number of individuals and groups that has assures the eventual success of the Tranexamic Acid Comparison in Hip Replacement (TeACH-R). The contributions of Dr. Douglas Naudie, Dr. James Howard and the individuals listed below have been invaluable not only in the development of this trial, but also in my development as a prospective academic surgeon.

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1 Introduction

Blood conservation plays a very important role in the care of a patient with lower extremity joint replacement. The procedure mandates consideration as major orthopaedic surgery, where a significant amount of blood loss is expected both during and after surgery. Tranexamic acid (TEA), a drug used to reduce perioperative blood loss, has been touted as a valuable adjunct to many perioperative blood conservation protocols. However, some concern remains over the efficacy and safety of the drug in hip replacement surgery. This thesis will outline the development and results of a prospective randomized clinical trial (RCT), the TeACH-R trial. The primary goal of this trial is to assess the comparative efficacy of TEA administered via two distinct routes, topical and intravenous, in decreasing blood loss after total hip arthroplasty (THA). The following chapter outlines important clinical considerations leading to the development of the TeACH-R trial.

1.1 Osteoarthritis

Osteoarthritis (OA) is characterized as progressive degenerative change resulting in articular cartilage loss within a joint. Cartilage erosion results from altered joint motion. In the lower extremity, the larger weight-bearing joints (the hip and knee) are affected more often than the smaller joints of the foot and ankle. Osteoarthritis results in full thickness, complete articular cartilage loss, with changes extending to the subchondral bone. Reactive osteophytes and bony sclerosis cause symptoms of stiffness, impingement and pain with weight bearing. Soft-tissue structures are also affected by changes within the bony architecture. Chronic inflammatory changes within the synovium cause hypertrophy, in addition to ligamentous laxity and muscle weakness resultant from disuse and altered biomechanical forces within the joint.[1]

The etiology of osteoarthritis is multifactorial, including both genetic and environmental influences. Any joint in the body can be affected. A number of pathologic and anatomic changes can lead to osteoarthritic changes. Although most commonly presenting in idiopathic fashion without any identifiable cause (primary osteoarthritis), trauma, osteonecrosis or congenital disorders are all secondary causes that can predictably lead to degenerative changes. Typically, the disease presents in middle age, although it can be earlier if secondary causes are suspected. Known risk factors for the development of hip and knee osteoarthritis include advanced age, obesity, previous trauma or deformity in the affected joint, and joint instability[1]. Pain and stiffness are the most frequent clinical symptoms expressed by sufferers of the disease. Loss of active and passive range of motion at the affected joint is the most relevant clinical sign. Radiographically, the disease is defined by progressive joint space loss, often in association with osteophytosis, sclerosis along the joint line, and subchondral cyst formation. The complete clinical picture, in association with radiographic findings, determines the need for treatment.

A number of non-operative treatment options are available to the clinician treating patients suffering with arthritis. Although the principles of osteoarthritis treatment are generalizable to almost any joint, sufferers of lower extremity knee and hip osteoarthritis deserve special consideration as weight-bearing joints. Conservative options attempt to offload the affected joint, or compartment within the joint. These include activity modification, weight loss, and functional bracing to compensate for altered force vectors acting at the level of the joint. Furthermore, supplementing with non-invasive pharmacologic agents helps in treating joint-related pain. Anti-inflammatories, including non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, are mainstays in the non-operative management of osteoarthritis with reliable therapeutic efficacy and favorable side effect profile. Corticosteroid injections into the affected joint can also provide a significant amount of pain relief. It is important, however, to realize that all aforementioned treatment modalities are focused on management of pain-related symptomatology. Although these help in delaying the need for operative intervention, they do not halt the progression of disease. A high percentage of patients treated conservatively for hip and knee osteoarthritis eventually progress to joint replacement surgery due to incapacitating pain and disability unresponsive to conservative therapy. In

Ontario, the burden of disease is significant: health care costs are 2 to 3 times higher, and quality-of-life is consistently rated 10 to 25 percent lower in individuals with osteoarthritis.[2] Worldwide, it is estimated that 10 percent of all people over the age of 60 years suffer from OA. It has proven difficult to reliably assess the proportion of people with OA who progress to THA, but there is evidence that the prevalence of OA does increase with age[3]. With the aging population, the economic and social burden of osteoarthritis is ever increasing.

1.2 Lower Extremity Arthroplasty

In the medical nomenclature, joint replacement surgery is termed arthroplasty: *arthr(o)-* defined as "relating to a joint" and *–plasty*, of Greek origin "to form"[4]. Practically, arthroplasty refers to the operative reconstruction or replacement of a diseased joint. The term arthroplasty is all encompassing, often used to denote a variety of joint-related reconstructive procedures. It is helpful to consider that all joints have two articulating cartilaginous surfaces. Joint reconstruction implies resurfacing or replacing both articulating surfaces of a joint. Often, like in THA, there is resection of supportive bone mass along with the articular surface prior to implantation of the prosthesis.

Three bony articulations in the lower extremity are prone to degenerative changes requiring reconstructive surgery: the ankle (tibio-talar) joint, the knee (tibio-femoral and patellofemoral) joint and the hip (femoroacetabular) joint. Severe degenerative changes, in association with debilitating symptoms and decreased quality of life, are indications for joint replacement. The focus of this dissertation is on reconstruction of the hip joint. The surgical procedure, as described in the following section, involves complete resection of the femoral head and neck, with concomitant resurfacing of the acetabular articular surface.

1.2.1 Total Hip Arthroplasty

Primary total hip arthroplasty continues to help a great number of individuals who suffer from OA. The 2014 Canadian Joint Replacement Registry Annual Report states that

24,515 primary total hip replacements were performed across Canada in 2012-13[5]. As can be seen in Figure 1.1, the vast majority of primary THA performed in Canada are for a diagnosis of primary osteoarthritis.
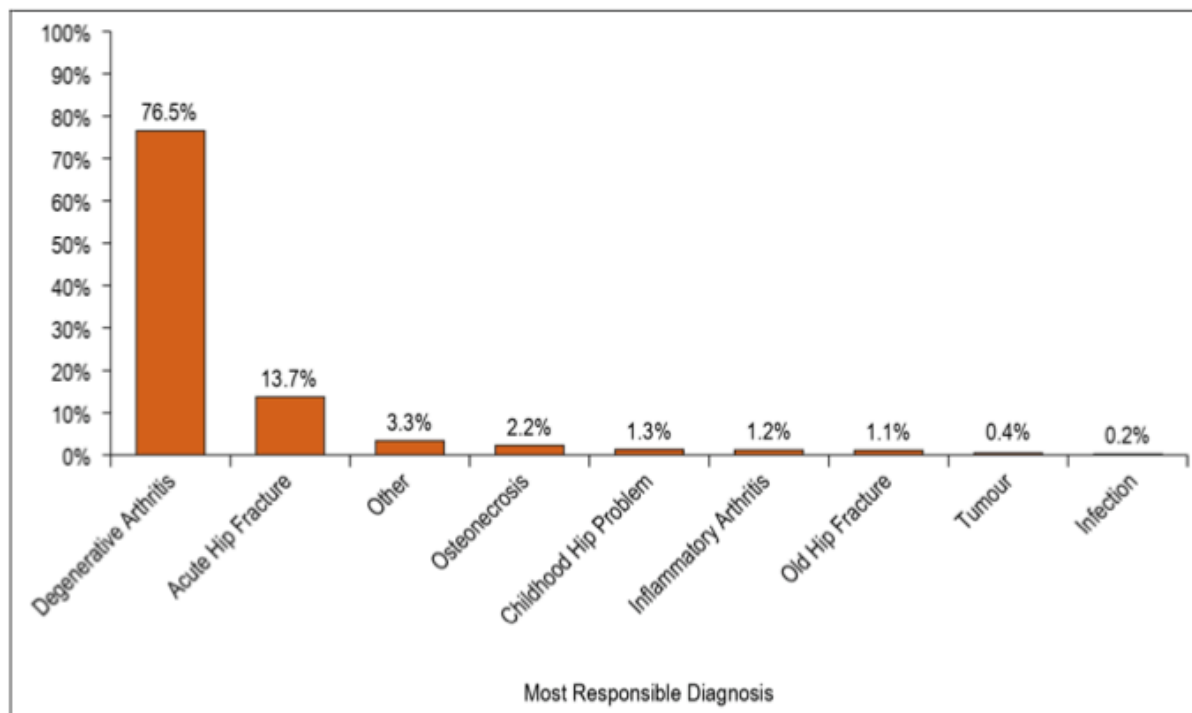
Figure 1.1: Most Responsible Diagnosis for Primary Total Hip Replacement, fiscal year 2012-2013. (Reproduced with permission from the Canadian Joint Replacement Registry 2014 Annual Report, www.cihi.ca/cjrr)

Success of THA can be defined in many ways. From the patient perspective, satisfaction is usually excellent after primary THA if the indication for surgery is for the relief of pain associated with osteoarthritic changes within the joint. Quality of life reliably improves after THA. From the standpoint of implant longevity, survivorship of most implant systems is approximately 95% at 10-year follow-up[6, 7]. Overall, THA offers those with end-stage degenerative hip disease a viable surgical option with predictably good outcomes. However, it is considered a major intervention, putting the patient at risk both during the procedure and throughout the postoperative course. Although the expected benefits are significant, careful patient selection and preoperative medical optimization is paramount in order to gain the most benefit with minimal risk.

1.2.1.1   Surgical Technique

The modern age of THA comes after many fundamental changes in implant design and materials engineering. However, the surgical technique remains similar to the low-friction arthroplasty described by Sir John Charnley in the 1962[8, 9].

The bones of the hip joint lie deep in the area of the pelvis beneath a number of important soft tissue structures, including muscles, tendons, nerves and arteries. There are many described surgical approaches to exposing the femoral head and acetabulum safely. The three main surgical approaches commonly used in North America are the modified direct lateral (Hardinge) approach, the posterior (Southern-Moore) approach and the direct anterior (Smith-Peterson or Heuter) approach. At London Health Sciences Center, University Hospital (LHSC-UH), the most common approach is the modified direct lateral approach. In his original publication, Dr. Kevin Hardinge describes the approach with the patient laying supine on the operating table[10]; the modified Hardinge approach uses lateral decubitus positioning to aid with visualization. Proponents of using this approach cite adequate operative exposure, with a very low rate of prosthetic dislocation of the implant in the postoperative period. Disadvantages are related to the trans-muscular nature of the approach and limited visualization of the acetabulum. Consequently, there is potential to increase surgical bleeding as a result of injury to the perforating arteries located within the muscular layers of the upper thigh, as described in Section 1.3.1.

Graphical representation of the modified Hardinge surgical approach to the hip joint is outlined in Figure 1.2. Starting with a lateral skin incision centered over the greater trochanter, sharp dissection proceeds through the subcutaneous fat layer to reveal the fascia of the gluteal musculature, thickening distally to form the iliotibial (IT) band. A longitudinal incision through the IT band and fascia allows identification of the gluteus medius musculature overlying the anterolateral aspect of the proximal femur. In the next tissue layer, a split in the gluteus medius muscle belly in line with its muscle fibers overlying the femoral neck allows identification of gluteus minimus. An incision is made through the tendinous portion of gluteus minimus and the capsule overlying the femoral neck. Reflection of the gluteus medius and vastus lateralis off the anterior aspect of the

femur allows visualization of the entire proximal femur. After release of periarticular structures, surgical dislocation of the femoral head allows enough visualization to properly landmark the femoral neck osteotomy site approximately one centimeter above the lesser trochanter. Once the osteotomy is completed, the femoral head is excised and the shaft of the proximal femur translated posterolaterally. The floor of the acetabulum is then visible, and preparation of the femoral and acetabular surfaces for implantation of the prosthesis can proceed.
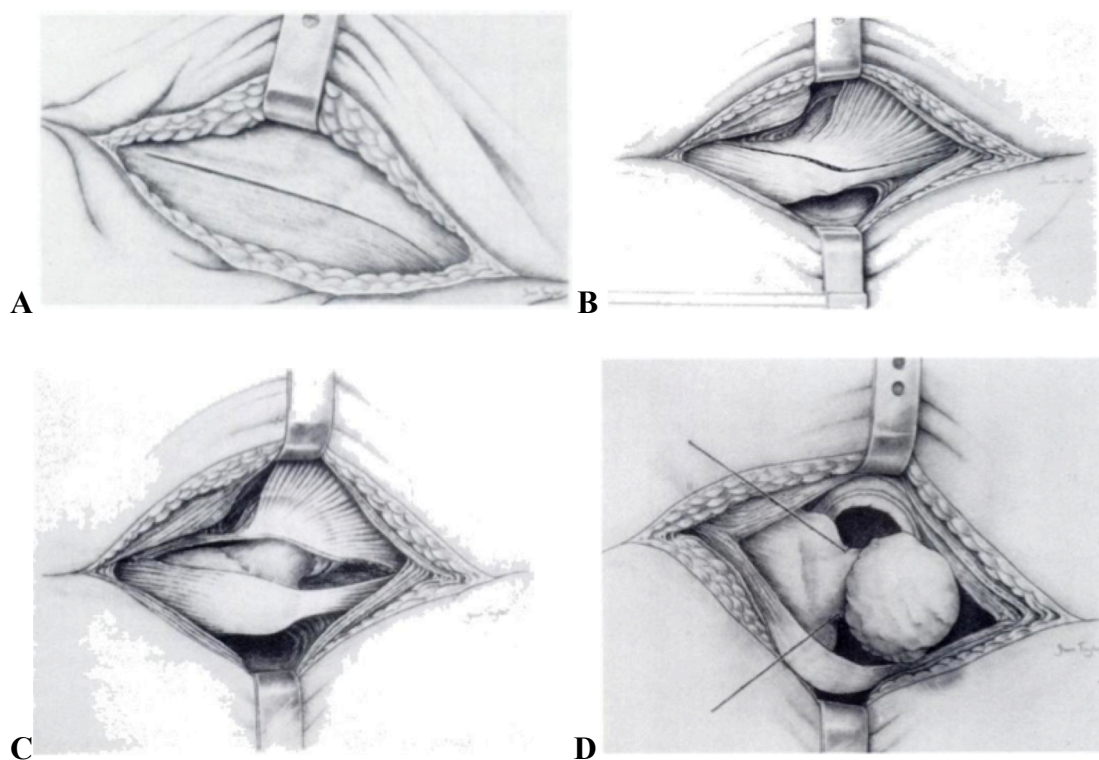
Figure 1.2: Modified Direct Lateral (Hardinge) Approach to the Hip Joint. After the skin incision, an incision is made through the IT band and gluteal fascia (**A**). The gluteus medius is divided, leaving a tendinous cuff attachment to the greater trochanter (**B**), exposing the gluteus minimus and capsular tissue layers (**C**). Further incision through the gluteus minimus and capsule, followed by elevation of a muscular flap off the anterior proximal femur, allows dislocation of the femoral head and preparation for the femoral neck osteotomy (**D**). (Reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery from Hardinge, K. *J Bone Joint Surg Br* 1982; 64-B(1): 17-19)

Although cement fixation of femoral and acetabular components was common practice in the past, and still has a role in primary THA for hosts with poor capacity for bony ingrowth, cementless (press-fit) fixation is the popular choice for the majority of North American surgeons. The sequence of preparation of the femoral neck osteotomy and acetabular surfaces for implantation of cementless implants is surgeon-dependent. For the acetabulum, all soft tissues, including the labrum, are excised to reveal the entire articular surface. Reaming of the acetabulum, a process of excising degenerative acetabular cartilage and sclerotic bone using sequential reamers of increasing diameter, allows the creation of a bed and surrounding rim for fixation of the press-fit shell. This shell will hold a highly cross-linked polyethylene liner, the acetabular bearing surface. On the femoral side, the intramedullary canal is first identified, and preparation of the canal allows for sizing of the final prosthesis. Rotational and axial stability of the femoral implant is due to a secure fit of the prosthesis within the proximal femur. Modern implants have a modular femoral head component sitting on the femoral stem at the head-neck junction. Trialing of various femoral head lengths allows for appropriate sizing. This critical step is necessary in order to maintain appropriate implant stability, keeping in mind the patient's soft tissue tension and leg length. Once the final components are selected, implantation ensues, with subsequent closure of all tissue layers to complete the operative procedure.
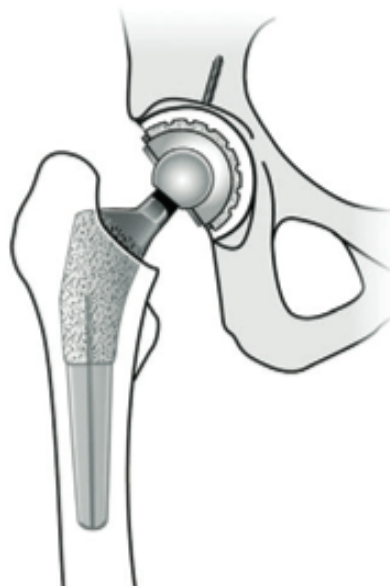
Figure 1.3: Modern Cementless Total Hip Implant (*in situ*). The femoral component is press-fit into the proximal metadiaphyseal portion of the intramedullary canal. The modular femoral head component articulates with the liner. The acetabular shell is firmly seated into the reamed acetabulum. (Reproduced with permission and copyright © from Pivec, R et al. *Lancet* 2012; 380: 1768-77)

1.3 Blood Loss During and After Total Hip Arthroplasty

Despite the best intentions of the treating orthopaedic surgeon, complications are occasionally seen after THA. Clinically significant blood loss often presents insidiously. The soft tissues in and around the hip, notably the significant adiposity in the subdermal layers of the thigh, make the THA patient vulnerable to a significant amount of unrecognized blood loss during and after the operative procedure. Unlike in total knee arthroplasty (TKA), a tourniquet cannot be applied prior the operation given the proximal nature of the skin incision. Best efforts to maintain intraoperative hemostasis are taken by the treating surgeon and anesthesiologist, in order to reduce bleeding into the postoperative period.

1.3.1 Sources of Blood Loss During Total Hip Arthroplasty

Importantly, bone ends that have been osteotomized have a propensity for continued bleeding into the postoperative period. Unfortunately, the surgeon has limited options for

dealing with bleeding from vessels contained within bone, as neither electro-cautery nor suture ligation is effective at arresting the persistent ooze emanating from cancellous bone. Both the femoral intramedullary canal and the periacetabular region contain a significant amount of cancellous bone. In THA, bony blood loss arises from both the femoral neck osteotomy site and subchondral bone on the acetabular surface after the latter has been reamed. Although implantation of final components in press-fit fashion does provide a mechanism for local tamponade of bleeding bone, in the absence of a competent clotting cascade continued hemorrhage may be significant enough to require transfusion of packed red blood cells, either autogenic or allogeneic. Moreover, the direct lateral approach, trans-muscular by definition, does place the perforating intramuscular branches of the femoral arterial system at risk of injury. Ruptured intramuscular arteries can retract into the muscle bed, making it particularly difficult to grasp and ligate the ends of the injured vessel intraoperatively. The above can occur without any overt external blood loss or hematoma formed in the visible superficial tissues surrounding the hip joint. It is this slower, persistent bleeding that is targeted with the administration of antifibrinolytic agents in the perioperative period, as described in Section 1.4 and 1.5.

Thankfully, vascular injury to the main branches of the iliac, femoral or obturator vascular system remains a rare complication of THA, estimated at 0.25%[11], usually as a result of aggressive retractor placement in the antero-superior acetabulum and proximal femur. The placement of acetabular screws is also a risk factor for intraoperative bleeding given the relative proximity to major blood vessels, as seen in Figure 1.5. Deep drill or screw penetration can lead to vascular penetration, thrombosis, and significant amounts of intra-pelvic blood loss. Although rare, this does represent another source of blood loss in THA. Antifibrinolytics do not target these causes of massive intraoperative hemorrhage.

M. Iliopsoas

M. Sartorius

M. Rectus femoris

1.

N., A., V. Femoris

M. Pectineus

A

Ramus capsularis
A. circumflexae femoris
lateralis

Rami nutritii
Colli et capitis

A. Femoralis

A. Circumflexa femoris
medialis

A. Profunda femoris

A. Circumflexa femoris
lateralis

Trochanter minor
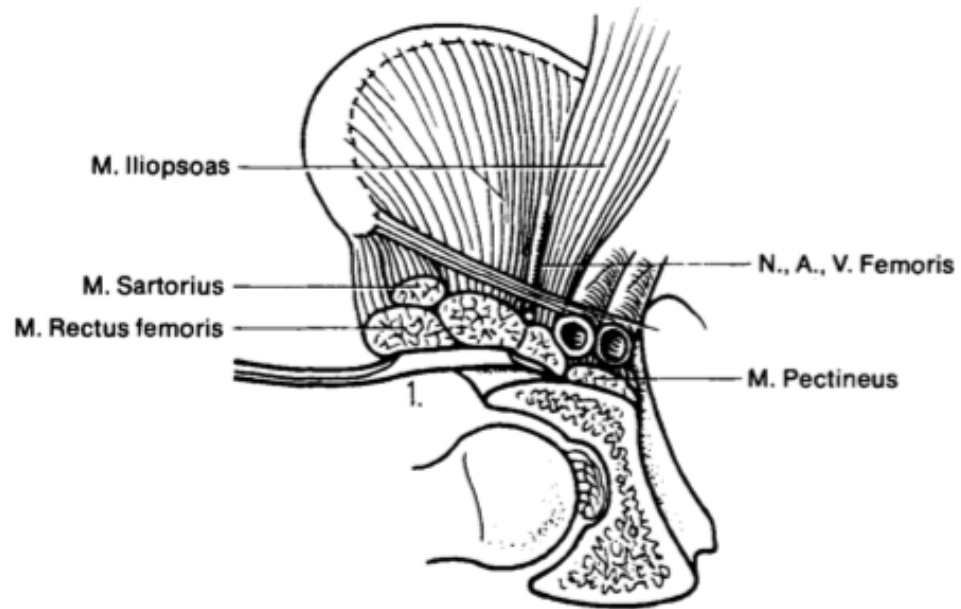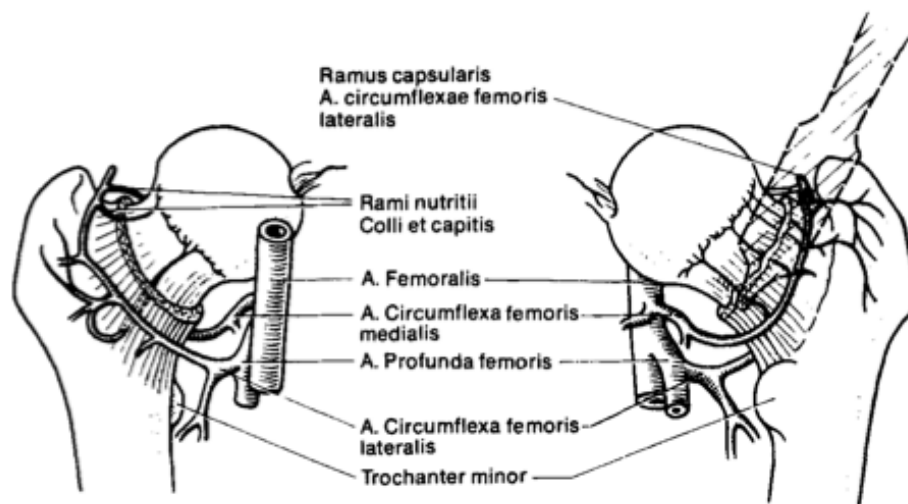
B

Figure 1.4: Common Femoral Artery and Major Branches Around the Hip.
Proximal (**A**) and distal (**B**) extension of the external iliac and common femoral artery is visualized above. Important anatomic relationships of relevance to the surgical approach for the hip are noted. The smaller branches of the femoral arterial system are at risk during the direct lateral surgical approach. (Reproduced from Nachbur, B et al. *CORR* 1979; 141: 122-132)
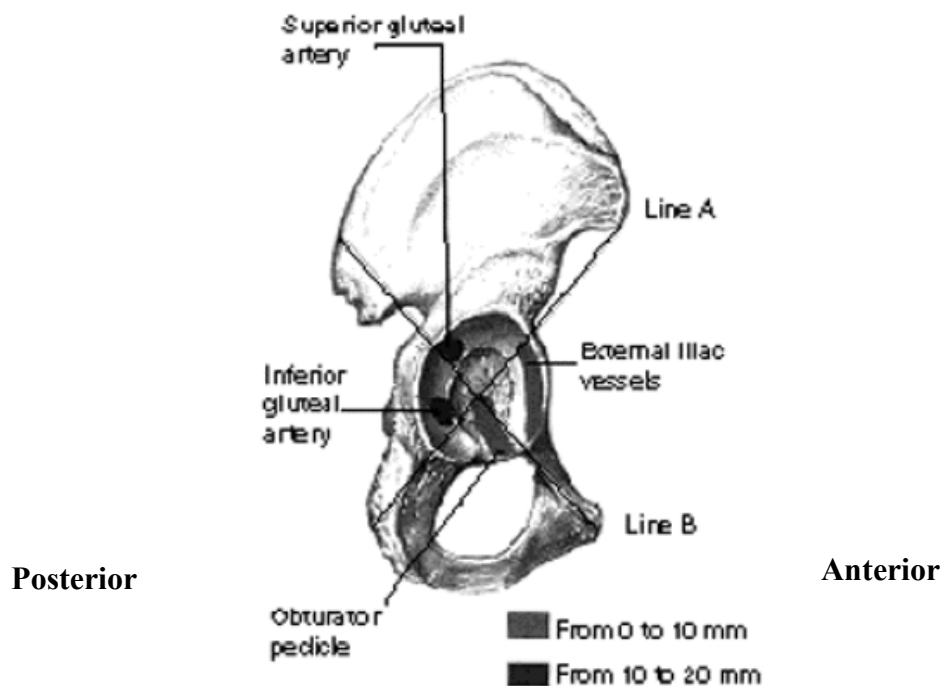
Figure 1.5: Relationship of Pelvic Vascular Structures to Surface Acetabular Landmarks. For acetabular screw placement, the "safe zone" corresponds to the postero-superior quadrant of the acetabulum, where the only vascular risk is the superior gluteal artery. "Danger zones" correspond to the antero-superior and antero-inferior quadrants, where the external iliac vessels and obturator pedicle lie in close proximity to the acetabular fossa. (Reproduced with permission and copyright © from Springer, Feugier, P et al. *Surg Radiol Anat* 1997; 19(2): 85-90)

1.3.2 Physiologic Response to Surgical Blood Loss

The human response to blood loss is predictable. If hypovolemia due to hemorrhage is significant, the initial response is to maintain cardiac output. Until hypovolemia is corrected, a decrease in cardiac preload results in a decrease in stroke volume. Heart rate increases proportionally to compensate for the lack of intravascular volume, and systemic vascular resistance decreases to reduce cardiac afterload. Although transport of oxygen is presumed to be negatively affected by an acute loss of red blood cell mass, Weiskopf et al showed that in healthy conscious volunteers at rest, a drop in hemoglobin to 50 mg/dL did not result in a significant drop in oxygen carrying capacity or clinically significant tissue hypoxia[12]. Although these represent important findings, the stress of major

orthopaedic surgery in the elderly arthroplasty patient is likely to produce significant biochemical changes affecting that individual's physiologic capacity to respond to acute or subacute blood loss.

The coagulation and fibrinolytic systems are the keystones of the human body's inherent hemostatic mechanism. Both pathways are termed cascades because of the hierarchical activation of serine proteases. One receptor-ligand interaction triggers a coordinated set of downstream reactions, eventually leading to a stable clot. The dynamic interplay between coagulation and fibrinolysis attempts to seal a bleeding vessel, while maintaining enough patency of the vascular lumen to allow nutrient delivery to downstream tissues. Coagulation, as the name implies, performs the former function and occurs by interacting closely with the initial platelet plug to form a stable complex of macromolecules, or clot, over bleeding vessels. Fibrin, the active form of the pro-peptide fibrinogen, plays an important role in the process of coagulation, forming an intricate network of cross-linked fibers within the platelet plug to form an insoluble clot. On the other hand, fibrinolysis acts to break down this clot in order to maintain a patent intravascular lumen. Here, plasmin plays a key role in breaking apart the cross-linked fibrin. These cascades are outlined in Figure 1.6.

Although the *intrinsic* pathway is an important contributor to coagulation, the *extrinsic*, or tissue factor-mediated coagulation pathway is predominantly responsible for the initiation and propagation of the coagulation cascade during and after surgical trauma. Tissue factor (TF), a macromolecule present in the subendothelial layer of blood vessels and in the extracellular environment, is not exposed to flowing blood unless there is vascular injury causing intimal damage. TF is the receptor for factor VII (FVII), the latter flowing freely in the bloodstream. FVII interact with TF only if TF becomes exposed to flowing blood; upon binding, FVII becomes activated (FVIIa), and subsequently interacts with factor X (FX). FX, once activated, cleaves prothrombin to thrombin. Thrombin, in turn, cleaves fibrinogen to fibrin, the active monomer contributing to a highly cross-linked mesh able to stabilize the initial platelet plug. Thrombin also catalyzes the conversion of factor XIII (FXIII) to its active form (FXIIIa), which is a necessary cofactor for cross-linking of fibrin monomers[13].
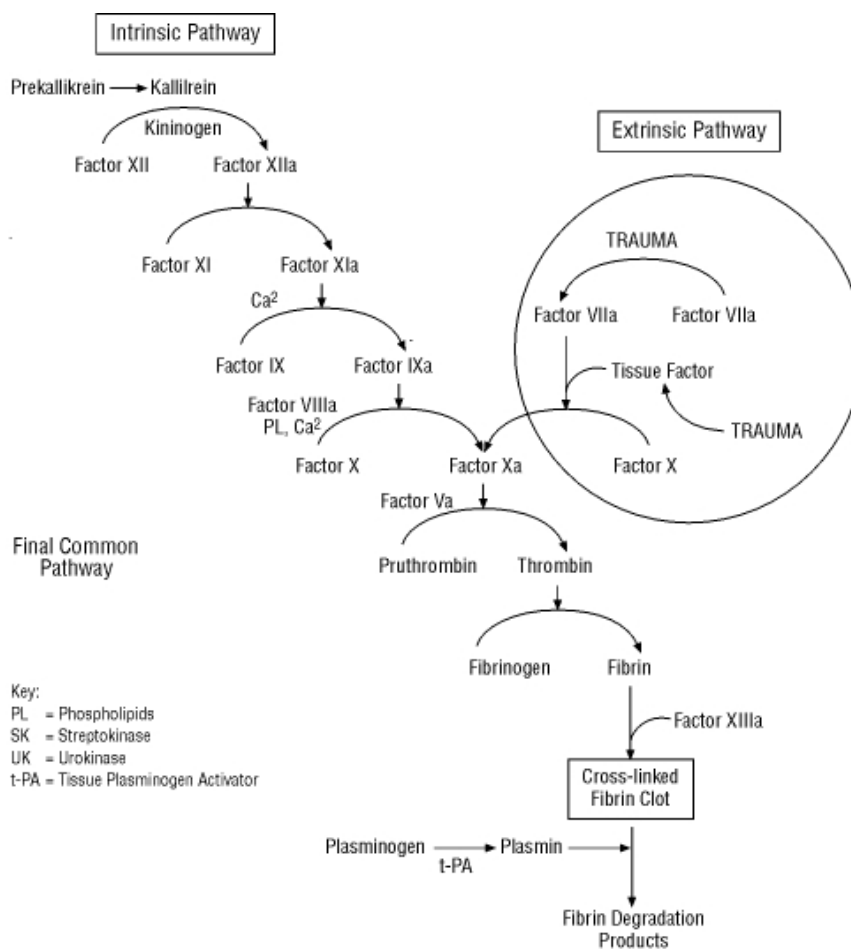
Figure 1.6: Overview of the Coagulation and Fibrinolytic Cascades. Tissue Factor is released when a blood vessel is injured. The subsequent cascade of serine proteases leads to the conversion of prothrombin to thrombin, which converts fibrinogen to fibrin. Under the influence of Factor XIIIa, fibrin monomers get cross-linked. Fibrinolysis occurs upon binding of tissue plasminogen activator (tPA) to plasminogen, with subsequent conversion to plasmin. Plasmin then degrades the fibrin clot, with formation of fibrin degradation products. (Reproduced from McGilvray, ID and Rotstein, OD. Surgical Treatment: Evidence-Based and Problem-Oriented. 2001. http://www.ncbi.nlm.nih.gov/books/NBK6959/)

Fibrinolysis is the counter-regulatory process that assures continued flow through the lumen of the bleeding vessel. Plasminogen is the inactive precursor of plasmin, circulating in the bloodstream. Conversion of plasminogen to its active form proceeds only once plasminogen binds to fibrin, where this zymogen adopts an open conformation. Only at this point is an activator, such as tissue plasminogen activator (tPA), able to bind the molecule and convert it to its active serine protease, plasmin. Plasmin can then act to

cleave the fibrin cross-links, destabilizing the formed clot in order to ensure vessel patency[14]. Fibrin degradation products (FDP) are formed upon cleavage of fibrin cross-links.

1.3.3   Hemostasis in Arthroplasty

Total knee and total hip arthroplasty produce a significant amount of tissue trauma. In TKA, postoperative hemostasis is largely influenced by the accelerated fibrinolytic reaction at time of tourniquet release[15, 16]. The same is not seen in THA, as tourniquet application is not possible when operating on the hip joint. Initiation of the coagulation cascade, with concurrent activation of the fibrinolytic system, begins from the time of initial of tissue trauma. The surgeon is dependent on a number of surgical techniques to control blood loss in the surgical field during THA. Suture ligation, electro-cautery and the application of synthetic sealant products and tissue glues are valuable tools available to the surgeon attempting to achieve intraoperative hemostasis. Watertight closure techniques with the concomitant goal of decreasing dead space between tissue layers can also decrease the space available for collection of blood in the potential spaces around the hip joint. The anaesthesia team has a key role in identifying and treating surgical hypovolemia. The administration of intravenous resuscitative fluids, vasoactive medications and the control of blood pressure contribute significantly to reducing intraoperative blood loss. However, as mentioned in Section 1.3.1, not all sources of intra-operative blood loss are amenable to correction via these modalities.

Bleeding in the postoperative period is further potentiated by the need for anticoagulation after lower extremity total joint arthroplasty. Total hip and knee arthroplasty are considered procedures that carry a moderate-to-high risk of postoperative thromboembolic events. A deep vein thrombus (DVT) can migrate proximally throughout the venous system to cause pulmonary emboli (PE), both considered major venous thromboembolic events (VTE). If large enough in size, PEs can lodge in the pulmonary arterial tree, resulting in a ventilation-perfusion mismatch. If the area of lung affected is large, or in the event of the dreaded saddle embolus blocking the confluence of the right and left pulmonary arteries, this can be a fatal complication of elective surgery. Commonly, a direct thrombin inhibitor such as rixaroxaban, or an agent in the low-

molecular-weight heparin class such as dalteparin is indicated for the purpose of decreasing the incidence of these important, potentially life-threatening postoperative complications. In respective guideline statements, the American College of Chest Physicians and the American Academy of Orthopaedic Surgeons both strongly endorse thromboembolic prophylaxis as standard of care after lower extremity total joint arthroplasty[17, 18]. In a recent randomized clinical trial published in the New England Journal of Medicine, major VTE occurred in only 0.2% of 1595 participants receiving rivaroxaban, an absolute risk reduction of 1.7% when compared to the treatment group receiving enoxaparin, another oft-utilized thromboprophylactic agent[19]. On the other hand, the incidence of asymptomatic DVT or PE is estimated at approximately 50% when prophylactic anticoagulation is not initiated in the postoperative period[20]. The contrasting results of these studies emphasize the need for effective thromboprophylaxis after THA.

Management of blood loss in arthroplasty is a significant challenge, not only because of difficulties in controlling the source of blood loss, but also because of a lack of therapeutic options in modulating the coagulation and fibrinolytic cascades to effectively decrease blood loss. In attempts to stop bleeding, maintaining vessel patency and avoidance of dreaded thromboembolic complications are also critical factors to consider in the perioperative care of the arthroplasty patient. Blood conservation protocols reflect these goals of treatment.

1.4 Perioperative Blood Conservation

1.4.1 Preoperative Anemia in the Total Hip Arthroplasty Patient

The adverse effects of blood loss are complicated by the relatively high incidence of preoperative anemia in the arthroplasty patient population. It is estimated that approximately 25 to 45 percent of patients proceeding to THA or TKA are anemic pre-operatively[21]. Preoperative use of NSAIDs causing subacute gastrointestinal blood loss and anemia of chronic disease are prevalent etiologies for anemia in the arthroplasty patient. Preoperative anemia has been cited as a risk factor for postoperative infection, transfusion, and even mortality[21]. In a landmark paper, Carson determined that "the

effect of blood loss on mortality was larger in patients with low preoperative hemoglobin than in those with a higher preoperative hemoglobin."[22]

The presence of concurrent medical comorbidities mandates a thorough preoperative medical review as a part of the evaluation of the perioperative evaluation for the arthroplasty patient. Management of preoperative anemia, in particular, plays a large role in medical optimization prior to total joint arthroplasty. As mentioned in Section 1.3.2, decreased oxygen carrying capacity from low red blood cell mass decreases the potential for aerobic metabolism in downstream tissues, increasing the risk for end-organ ischemia. Although this may not be a factor in young, healthy individuals, the typical elderly arthroplasty patient does not meet these criteria. The heart is particularly vulnerable in this patient population. The presence of ischemic heart disease, in addition to concurrent pharmacologic treatment with cardiogenic medications, decreases the intrinsic physiologic response to surgical stress.

1.4.2 Risk of Perioperative Transfusion

It is now understood that allogeneic transfusion for the treatment of anemia related to surgical blood loss should be avoided when possible. In addition to cost and resource constraints, the current evidence shows an increased risk of surgical site, urinary tract and respiratory tract infections in patients that receive allogeneic blood in the postoperative period[23-26]. Ongoing concerns regarding the safety of transfusing stored blood products have ushered in the use of restrictive transfusion algorithms for surgical patients, showing significant clinical benefit over the liberal transfusion of blood products in a number of high-quality studies in surgical and critically ill patients[22, 27, 28]. A restrictive transfusion algorithm is in use at LHSC-UH; further details are provided in Chapter 3.5.3.

1.4.3 Blood Conservation Modalities

A multidisciplinary approach to blood conservation in total joint arthroplasty is paramount to optimal perioperative care of the arthroplasty patient. Although there exists

some heterogeneity in blood conservation protocols across centers, several common themes are present.

Pharmacologic iron supplementation and the use of erythropoietin-stimulating agents (ESA) increase red cell mass prior to surgical intervention, with good efficacy and reasonable safety profiles[21]. Both can have significant clinical benefits, especially if started over 3 weeks prior to surgery[29]. Whereas iron supplementation has proven benefit with general ease of administration preoperatively, ESA can be a costly modality reserved for patients meeting strict diagnostic criteria. Preoperative autologous blood transfusion, intraoperative cell salvage, and postoperative blood reinfusion strategies are moderately effective, and have been used as part of perioperative blood conservation protocols in the past. However, these have decreased in popularity as a result of modalities that are less resource-intensive and of similar efficacy and safety[30, 31]. A number of studies in both hip and knee arthroplasty have affirmed the clinical utility of antifibrinolytic agents, such as TEA, in reducing blood loss in the perioperative period. As evidenced in the following sections, these represent promising adjuncts to traditional blood conservation protocols, especially for the patient at risk of significant intraoperative blood loss.

1.5 Antifibrinolytics

The use of antifibrinolytic therapy in surgery has grown due to a number of inciting factors and events. In recent years, the ever-increasing cost and incidence of transfusion-related complications has ushered in widespread reluctance to the use of blood products in the perioperative setting. Consequently, medical and surgical teams managing of the perioperative care of patients having surgical interventions with an elevated risk of blood loss have developed blood conservation protocols to decrease the reliance on allogeneic blood products for the treatment of surgical anemia. Antifibrinolytics, such as TEA, epsilon-aminocaproic acid (EACA) and aprotinin, were first identified as useful adjuncts in cardiothoracic interventions, where a counter to the potent fibrinolysis-inducing effect of cardiopulmonary bypass was sought by surgeons and anaesthesiologists seeking better

control of perioperative bleeding. After a number of high-quality studies showed good clinical effect with minimal risk to the patient[32-34], orthopaedic surgeons began to institute antifibrinolytics prior to and during procedures carrying a significant risk of blood loss, lower extremity total joint arthroplasty included. The following section provides an overview of the pharmacology inherent to antifibrinolytic therapy, and its role in the perioperative care of the arthroplasty patient.

1.5.1 Lysine Analogues: Tranexamic Acid and Epsilon-Aminocaproic Acid

Tranexamic acid and epsilon-aminocaproic acid comprise the lysine analogue class of antifibrinolytic agents. They have identical mechanisms of action, with TEA displaying a six- to ten-fold increased affinity compared to the EACA moiety[35, 36]. Owing to its high affinity and comparatively low cost, TEA has largely replaced EACA as the predominant lysine analogue used in major orthopaedic procedures.

Lysine analogues prevent fibrinolysis. The structural similarity to the amino acid lysine allows the drug to bind the lysine-binding site on plasminogen. Under normal circumstances, plasminogen is a promoter of fibrinolysis when combined with tPA. Plasminogen subsequently gets converted to plasmin, with the active lysine-binding site on plasmin now able to interact with the active receptor on fibrin. Plasmin can then break down cross-linked fibrin and dissolve insoluble mesh of fibrin holding the clot together. TEA acts as a competitive inhibitor of plasminogen via action at this fibrin-binding site. Plasmin can no longer bind fibrin when TEA is bound to the lysine-binding site. Fibrin remains cross-linked, stabilizing the formed clot and promoting local hemostasis (Figure 1.7).
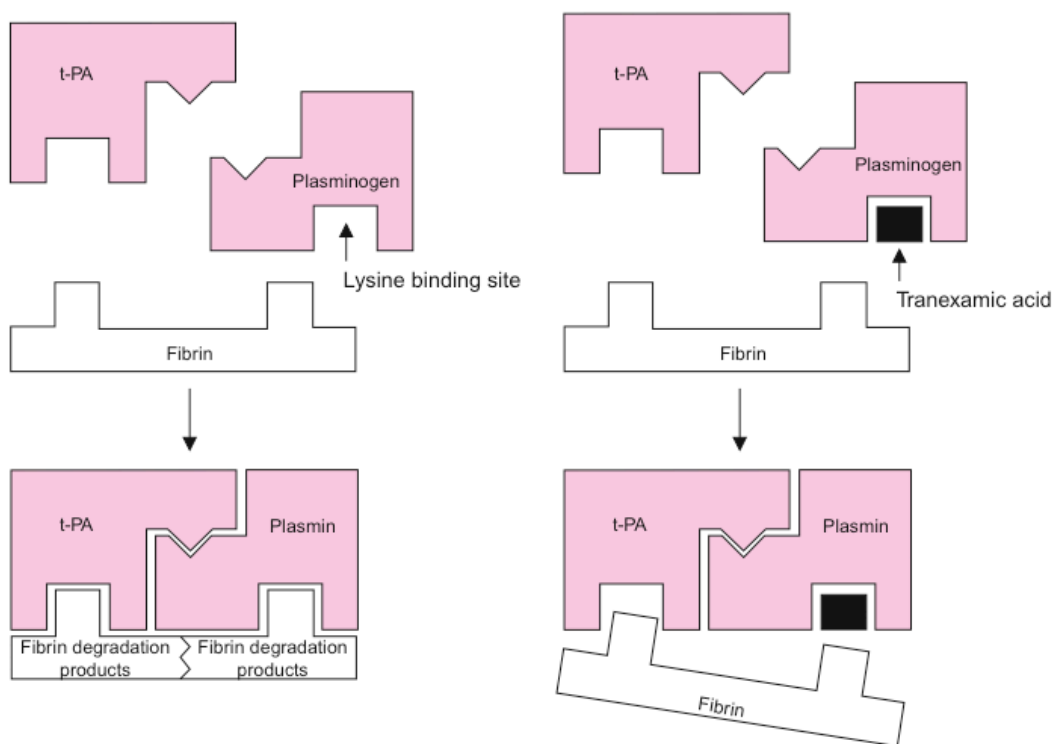
Figure 1.7: Mechanism of Action, Tranexamic Acid (and Epsilon-Aminocaproic Acid). Due to structural similarities to lysine, both tranexamic acid and epsilon-aminocaproic acid moieties competitively inhibit binding of fibrin to plasminogen via interaction at an active lysine-binding site. Fibrinolysis is prevented, with concomitant stabilization of the fibrin clot. (Reproduced with permission from Dunn, CJ and Goa, KL. *Drugs* 1999; 57: 1005-1032)

The pharmacokinetic properties of the lysine analogues make this class of medication ideal for decreasing the short-lived intra-articular fibrinolytic response after lower extremity joint replacement surgery. Both molecules rapidly diffuse across tissue planes, and are able to reach effective concentrations within the joint shortly after intravenous administration. Studies in cardiac surgery have elucidated the pharmacokinetic and pharmacodynamic properties of intravenous TEA, sought after in attempts to find the safest and most effective dose. It has been determined that the distribution and elimination of TEA follows first-order kinetics, with a half-life of roughly 2 hours. TEA is not bound to proteins in the systemic circulation, and is rapidly excreted in urine largely unchanged in chemical structure. A serum concentration of 10-15 μg/mL

decreases fibrinolytic activity of plasmin by approximately 80%[38]. Also, when administered via the topical or intra-articular routes, systemic absorption of TEA is reduced by approximately 70% of the equivalent intravenous dose[39]. Because of renal elimination, dose adjustments are necessary in those with decreased kidney function, but not in those with hepatic impairment[35, 36]. Other side effects, as well as local and systemic allergic reactions are rare complications of antifibrinolytic administration.

1.5.2   Plasmin Inhibitors: Aprotinin

Aprotinin, a thrombin inhibitor derived from bovine lung tissue, has also been in total joint arthroplasty. Its activity on the fibrinolytic cascade has yet to be fully elucidated, although it is postulated to exert most of its clinical effect indirectly by decreasing the activation of factor XII through an inhibitory effect on the kallikrein pathway. The proteolytic activity of plasmin is also inhibited by aprotinin directly, although the mechanism is unclear[40].

In 2008, use of aprotinin was restricted in a number of countries, including both Canada and the United States, as a result of increased mortality when used in cardiac surgery. These results emanated from a large multi-center study, the Blood Conservation using Antifibrinolytics in a Randomized Trial (BART)[41]. These same findings were not present when TEA was used for this same purpose. Within the past two calendar years, the European Medicines Agency and Health Canada have reinstated aprotinin for use in cardiac surgery, but only in cases where an excessive amount of blood loss is expected. Given the increased cost as well as safety concerns related to use of aprotinin, it is no longer routinely used as an antifibrinolytic agent in orthopaedic surgery.

1.6 Tranexamic Acid Administration in Total Hip Arthroplasty

TEA is a versatile drug that has been used with therapeutic success in bleeding trauma patients[42], gynecologic surgery, cardiac surgery[43, 44, 33, 45], thoracic surgery[34] and only more recently orthopaedic surgery. Administration via the oral, topical, intra-articular and intravenous routes is described in each of these surgical fields. As will be discussed

in Chapter 2, there is documented Level I evidence to support the use of TEA in both TKA and THA. Although these procedures are inherently different in many ways, a review of the available evidence in TKA is essential to understand the rationale in the TeACH-R study design and the need to assess the clinical efficacy for intra-articular administration of TEA in THA.

The comparative efficacy of intravenous and topical administration of TEA has never been assessed in patients undergoing THA. TeACH-R is the short form for the study entitled Tranexamic Acid Comparison in Total Hip Replacement, a study developed at LHSC-UH powered to detect a clinically significant change in the hemoglobin drop after THA. The purpose of the study is to perform a direct comparison of clinical efficacy between intravenous and topical administration of TEA, with the primary outcome measure of blood loss and drop in postoperative hemoglobin. The standard of care at LHSC-UH, based predominantly on results of a 2010 retrospective review by Ralley and colleagues, is to administer a single dose of 20 mg/kg of TEA intravenously 10 minutes prior to skin incision for THA[46]. This allows the solution to be infused completely before the start of the operation. The drop in hemoglobin postoperatively was lessened, with a concomitant decrease in the rate of postoperative allogeneic blood transfusion. However, an important study by Wong suggests that topical TEA administration in TKA has similar clinical benefit in terms of decreased blood loss and transfusion rate, with either a 1.5 gram or 3 gram single-bolus dose administered prior to tourniquet desufflation. In this study, plasma TEA levels drawn one hour after administration showed sub-therapeutic levels in the group receiving the 1.5 gram dose, indicating that even marginal plasma TEA levels can have good therapeutic effect in inhibiting the local fibrinolytic cascade without the risk that comes with elevated systemic load. To the best of the investigators' knowledge, a similar study has yet to be performed in THA, owing in large part to the lack of consistency in dosing and timing of administration in published studies examining TEA.

Direct antifibrinolytic action on bleeding vessels and a decreased risk of arthroplasty-related thromboembolic events (albeit theoretical) are potential advantages of administering TEA topically in THA. The TeACH-R investigators decided to administer

TEA topically at the time of arthrotomy closure, as it provides a reproducible method of administering the medication without interfering with surgical time while maintaining therapeutic activity. The goal is to target postoperative blood loss from intramuscular vessels and cancellous bone, in order to blunt the hemoglobin drop and reduce the need for transfusion of pRBCs. By allowing the TEA solution to bathe the joint while the tissue layers are closed in succession, the drug is then given a significant of time to exert its clinical action. A dose of 1.5 grams was chosen based on the results of previous studies showing no clinical benefit of a higher dose in total joint arthroplasty[39]. Blood loss and complications in TeACH-R study participants receiving this topical regimen are compared to single-bolus intravenous TEA administration at 20 mg/kg, the standard of care at LHSC-UH. Because the standard of care is an active agent with well-documented clinical efficacy, a placebo-controlled trial in this setting has significant ethical implications.

We hypothesize that administering topical TEA at the time of arthrotomy closure will not show a significant drop in the postoperative hemoglobin or perioperative blood loss when compared to intravenous TEA administered prior to the start of THA.

There is a significant body of evidence supporting the use of TEA over no antifibrinolytic therapy, whether it is administered intravenously or topically[47]. Proceeding with this study is part of the process of determining which is the most effective therapeutic regimen for administering TEA in THA. Not only will our results go a long way in optimizing blood conservation protocols for patients proceeding to THA at LHSC-UH, but this study will also allow others in the field to build on the current available knowledge base in order to gain the most clinical benefit of TEA while minimizing perioperative risk.

2 Literature Review

The following provides a brief overview of the relevant studies that have contributed to the gradual increase in popularity of TEA as a valuable adjunct in perioperative blood conservation programs. Only recently have appropriately powered clinical trials demonstrated clear benefit of administering TEA in both TKA and THA, regardless of whether the route of administration is intravenous (IV), intra-articular (IA) or topical.

2.1 Intravenous Tranexamic Acid in Total Knee Arthroplasty

Evidence supporting the use of TEA in lower extremity total joint arthroplasty first appeared in a small series of patients needing TKA, where Benoni et al showed that TEA would provide an effective counter to the hyperfibrinolytic reaction seen after tourniquet desufflation in TKA[15]. Ease of use and ability to administer serial doses of TEA were seen as advantages to administering the drug intravenously, although early reluctance to implementing TEA came from clinical studies that questioned the earlier claims of efficacy in decreasing blood loss after knee replacement surgery. Good et al assessed the effect of TEA on hidden blood loss in TKA using a 10 mg/kg dose of IV TEA given just before tourniquet release, concluding that the hemostatic agent reduced total blood loss and drain volume, but showed no discernable effect on reduction of hidden blood loss[48]. Larger, more recent studies have shown more promising results. A European clinical trial provided Level I evidence supporting the clinical and economical benefits of IV TEA in TKA, stating that use of TEA in the perioperative setting reduced blood loss by approximately 600 mL compared to placebo, making postoperative autologous reinfusion unnecessary and cost-prohibitive when a restrictive transfusion protocol is enforced concurrently[30]. In comparison to other traditional methods of intraoperative blood conservation, when two separate formulations of fibrin glue were compared to IV administration of TEA in a recent clinical trial, TEA was deemed to be the only effective agent in decreasing drain and calculated blood loss[49].

Although a general consensus exists supporting the benefits of IV TEA in TKA, significant heterogeneity exists between studies with regards to treatment regimens and outcome measures, making it difficult to reliably assess the true clinical effect of adjunctive antifibrinolytic therapy. The ideal protocol with regards to dosing and timing of administration has yet to be fully elucidated, although recent evidence suggests improved control of postoperative blood loss with serial administration of TEA during the perioperative period. In order to clarify this conflicting data, Maniar and colleagues designed a trial comparing four separate modes of TEA administration. In their study, patients receiving preoperative, intraoperative and postoperative administration of IV TEA at 10 mg/kg/dose had the least drain output and total blood loss compared to the group who received either one or two doses of the drug perioperatively, suggesting that serial dosing allows for optimal perioperative efficacy[50]. A prospective study by Alvarez et al also showed that a cohort of TKA patients receiving IV TEA as a bolus prior to tourniquet release supplemented by a 1 mg/hr infusion for 6 hours postoperatively had significantly decreased levels of drain and total calculated blood loss. In this study, the quoted number needed to treat to avoid one unit of blood transfused (autologous or allogeneic) is 9.2, further highlighting the efficacy of IV TEA in decreasing blood loss and rate of transfusion for patients having TKA[51].

Logistical barriers do, however, make timed serial dosing strategies and continuous bolus infusion difficult to administer, especially as the arthroplasty patient transitions to the postoperative recovery phase. There are single-bolus regimens that have shown to be safe effective and safe. A large-scale retrospective review of TKA cases performed before and after the implementation of a perioperative TEA protocol, consisting of a single IV TEA dose of 20 mg/kg prior to tourniquet release, showed significant reductions in hemoglobin drop and blood transfusion rates postoperatively[46]. The higher dose used in this protocol, much like other studies of relevance, did not show any clinically significant increase in thromboembolic complications.

2.2 Topical Tranexamic Acid in Total Knee Arthroplasty

There is also Level I evidence to support the use of topical TEA for reduction of blood loss after TKA. A recent clinical trial showed equivalent efficacy of a 1.5 and 3-gram topical TEA solution in reducing calculated blood loss by factor of approximately 25% compared to placebo[39]. In this study, a valuable addition to the clinical trial protocol is the biochemical analysis of plasma levels of TEA, measured one hour after administration in all treatment groups. The 1.5-gram topical dose resulted in significantly lower systemic load than the group receiving the higher dose, with no differences in the desired clinical effect. In a further attempt to contrast the effect of the different routes of administration on postoperative blood loss, Seo and colleagues published results of their three-armed prospective cohort study demonstrating modest improvements in hemostasis and drain output in the treatment arm receiving IA TEA, when compared to both IV TEA and placebo[52]. Although the latter group was only administered IV TEA after the surgical site was closed, this study provides further evidence in support of IA or topical administration of TEA in TKA. A review of recent studies examining the use of TEA in TKA is presented in Table 2.1.

Table 2.1: Selected Studies Evaluating the Use of Tranexamic Acid in Total Knee Arthroplasty.

Treatment Arms	Blood Loss	Transfusion	Complications
Good et al (2003)[48]			
1. IV TEA bolus 10 mg/kg at tourniquet release + repeat 10 mg/kg bolus 3 hours later; n=27. 2. Placebo; n=24	TEA < placebo (total) TEA = placebo (hidden)	TEA < placebo	TEA = placebo
Alvarez et al (2008)[51]			
1. IV TEA 1 gram bolus at tourniquet release + 1 mg/kg/hr infusion for 6 hours postop; n=46 2. Placebo; n=49	TEA < placebo	TEA < placebo (alloRBC) TEA < placebo (autoRBC)	NR
Ralley et al (2010)[46]			
1. IV TEA bolus 20 mg/kg bolus at incision; n=150 2. Placebo; n=145	TEA < placebo	TEA < placebo	TEA = placebo
Wong et al (2010)[39]			

Treatment Arms	Blood Loss	Transfusion	Complications
0. Placebo; *n*=35 T1. Topical TEA 1.5 grams at closure; *n*=31 T2. Topical TEA 3 grams at closure; *n*=33	T1 < placebo T2 < placebo T1 = T2	TEA = placebo	TEA = placebo
Charoencholvanich and Siriwattanasakul (2011)[53]			
1. IV TEA 10 mg/kg pre-tourniquet inflation + repeat 10 mg/kg bolus 3 hours postop + 500 mg TID orally x 5 days postop; *n*=50 2. Placebo; *n*=50	TEA < placebo	TEA < placebo	TEA = placebo
Maniar et al (2012)[50]			
0. Placebo; *n*=40 T1. IV TEA bolus 10 mg/kg at tourniquet release; *n*=41 T2. IV TEA bolus 10 mg/kg at tourniquet release + repeat 10 mg/kg bolus 3 hours postop; *n*=42 T3. IV TEA bolus 10 mg/kg prior to tourniquet inflation + repeat 10 mg/kg bolus at tourniquet release; *n*=42 T4. IV TEA bolus 10 mg/kg prior to tourniquet inflation + repeat 10 mg/kg bolus at tourniquet release + repeat 10 mg/kg bolus 3 hours postop; *n*=41 LA. Topical TEA 3 grams at closure; *n*=41	LA < T1 T3 < placebo T4 < placebo LA < placebo	TEA = placebo	TEA = placebo
Seo et al (2012)[52]			
1. IA TEA 1.5 grams at closure; *n*=50 2. IV TEA bolus 1.5 grams at closure; *n*=50 3. Placebo; *n*=50	IA < placebo IV < placebo IA < IV	IA < placebo IV < placebo IA = IV	IA = IV IA = placebo IV = placebo
Aguilera et al (2013)[49]			
1. BSTC Fibrin Glue; *n*=42 2. Tissucol; *n*=41 3. IV TEA bolus 1 gram x 2, first dose prior to tourniquet inflation, second dose prior to tourniquet release; *n*=41 4. Placebo; *n*=42	TEA < placebo TEA < fibrin	TEA < fibrin fibrin = placebo	TEA = fibrin = placebo
Georgiadis et al (2013)[54]			

Treatment Arms	Blood Loss	Transfusion	Complications
1. Topical TEA 2 grams at closure; *n*=50 2. Placebo; *n*=51	TEA < placebo	TEA < placebo	TEA = placebo
Konig et al (2013)[55]			
1. IA TEA 3 grams at closure; *n*=130 2. Placebo; *n*=29	TEA < placebo	TEA < placebo	NR
Alshryda et al (TRANX-K; 2013)[56]			
1. Topical TEA 1 gram at closure; *n*=79 2. Placebo; *n*=78	TEA < placebo	TEA < placebo	TEA = placebo
Oremus et al (2014)[30]			
1. IV TEA bolus 1 gram at incision + repeat 1 gram bolus 3 hours later; *n*=29 2. Placebo; *n*=27	TEA < placebo (intraoperative) TEA < placebo (drain loss)	IV TEA < placebo (autoRBC) IV TEA = placebo (alloRBC)	TEA = placebo

*IV: Intravenous TEA. IA: Intra-Articular TEA. AutoRBC: Autologous Blood Reinfusion. AlloRBC: Allogeneic Blood Transfusion. "<": Less than. "=": Equal to. NR: Not Reported.

2.3 Intravenous Tranexamic Acid in Total Hip Arthroplasty

Like in TKA, IV TEA has been shown to be effective, safe, and relatively easy to administer to patients undergoing primary THA. Appropriate timing of IV TEA administration is paramount. One of the first studies on the subject was a small double-blinded trial by Benoni, concluding no benefit with regards to blood loss when the drug was infused after implantation of the prosthesis[57]. A similar placebo-controlled study demonstrated that IV TEA administered prior to the start of the procedure showed significant benefit for both intra- and postoperative blood loss in the treatment group[58]. Although the sample size in these clinical trials is small, the contrasting results highlight the importance of appropriate timing of administration.

Variation also exists in the published protocols for IV administration of TEA during THA. There does not appear to be strong benefit of either a single-dose or multi-dose regimen when the drug is used in hip surgery. A retrospective review of five separate

regimens of IV TEA in THA showed benefit in decreasing drain output when administering the drug prior to skin incision with a repeat bolus dose 6 hours later[59]. In contrast, a study published in 2005 by Johansson demonstrated that a single dose of 15 mg/kg, given at the start of the procedure, is effective in decreasing calculated blood loss and the need for transfusion in the postoperative period[60]. Similarly, at our institution, we demonstrated a significant benefit with regards to decreased rate of transfusion when a single bolus dose of 20 mg/kg given prior to skin incision was used in THA. In this latter study, the postoperative drop in hemoglobin was attenuated in the cohort of patients having received IV TEA, in addition to an observed decrease in the rate of postoperative allogeneic blood transfusion[46].

2.4 Topical Tranexamic Acid in Total Hip Arthroplasty

Although limited, evidence supporting the use of topical TEA in THA continues to grow. Preliminary evidence emanating from a randomized controlled trial by Konig et al demonstrates that a protocol of topical TEA administered topically at three intraoperative steps during THA (after acetabular preparation, femoral broaching, and at closure of the arthrotomy) provides significant reductions in blood loss compared to placebo, with a negligible reduction in transfusion rate[55]. The European TRANX-H study also provides Level I evidence for use of topical TEA in primary THA, noting a significant decrease in transfusion rate in the group receiving 1 gram of topical TXA infiltrated into the joint prior to arthrotomy closure compared to placebo[56]. The evidence for routine use of topical TEA, however, lags behind the literature available for topical or intra-articular TEA in TKA. Higher-powered clinical trials are needed to further evaluate the efficacy and safety of administering TEA topically in THA. A review of recent studies examining the use of TEA in THA, administered both intravenously and topically, is presented in Table 2.2.

Table 2.2: Selected Studies Examining the Use of Tranexamic Acid in Total Hip Arthroplasty.

Treatment Arms	Blood Loss	Transfusion	Complications
Benoni et al (2000)[57]			
1. IV TEA bolus 10 mg/kg at closure + repeat 10 mg/kg bolus 3 hours later; *n*=20 2. Placebo; *n*=19	TEA = placebo	TEA = placebo	TEA = placebo
Ekback et al (2000)[58]			
1. IV TEA bolus 10 mg/kg at incision + repeat 10 mg/kg bolus 3 hours later; *n*=20 2. Placebo; *n*=20	TEA < placebo (intraoperative) TEA < placebo (postoperative)	NR	TEA = placebo
Husted et al (2003)[61]			
1. IV TEA bolus 10 mg/kg bolus at incision + 1 mg/kg/hr x 10 hours postop; *n*=20 2. Placebo; *n*=20	TEA = placebo (intra-operative) TEA < placebo (postoperative) TEA < placebo (total)	TEA < placebo	TEA = placebo
Garneti et al (2004)[62]			
1. IV TEA bolus 10 mg/kg bolus at incision; *n*=25 2. Placebo; *n*=25	TEA = placebo (intraoperative) TEA = placebo (postoperative)	TEA = placebo	TEA = placebo
Johansson et al (2005)[60]			
1. IV TEA bolus 15 mg/kg at incision; *n*=47 2. Placebo; *n*=53	TEA < placebo	TEA = placebo	NR
Niskanen et al (2005)[63]			
1. IV TEA bolus 10 mg/kg bolus at incision + repeat 10 mg/kg bolus q8h x 2; *n*=19 2. Placebo; *n*=20	TEA < placebo	NR	TEA = placebo
Yamasaki et al (2005)[64]			
1. IV TEA bolus 1 gram bolus at incision; *n*=21 2. Placebo; *n*=21	TEA = placebo (intra-operative) TEA < placebo (postoperative)	NR	TEA = placebo
Ralley et al (2010)[46]			
1. IV TEA bolus 20 mg/kg bolus at incision; *n*=109 2. Placebo; *n*=89	TEA < placebo	TEA < placebo	TEA = placebo

Treatment Arms	Blood Loss	Transfusion	Complications
McConnell et al (2011)[65]			
1. IV TEA bolus 10 mg/kg at incision; *n*=22 2. Fibrin spray; *n*=22 3. Placebo; *n*=22	TEA < placebo TEA = fibrin	NR	NR
Imai et al (2012)[59]			
T0. Placebo; *n*=22 T1. IV TEA 1 gram at closure; *n*=24 T2. IV TEA bolus 1 gram at closure + repeat 1 gram bolus 6 hours later; *n*=20 T3. IV TEA bolus 1 gram at incision; *n*=25 T4. IV TEA bolus 1 gram at incision + repeat 1 gram bolus 6 hours later; *n*=26	T3 < placebo (intraoperative) T4 < placebo (intraoperative) T3 < placebo (postoperative) T4 < placebo (postoperative)	TEA = placebo	NR
Alshryda et al (TRANX-H; 2013)[56]			
1. Topical TEA 1 gram at closure; *n*=80 2. Placebo; *n*=81	TEA < placebo	TEA < placebo	TEA = placebo
Konig et al (2013)[55]			
1. Topical TEA 3 grams in divided doses; *n*=91 2. Placebo; *n*=40	TEA < placebo	TEA < placebo	NR
Oremus et al (2014)[30]			
1. IV TEA 1 gram bolus at incision + repeat 1 gram bolus 3 hours later; *n=*20 2. Placebo; *n*=22	TEA = placebo (intraoperative) TEA < placebo (postoperative)	TEA < placebo (autoRBC) TEA = placebo (alloRBC)	TEA = placebo

*AutoRBC: Autologous Blood Reinfusion. AlloRBC: Allogeneic Blood Transfusion. NR : Not Reported.

2.5 Thromboembolic Risk of Perioperative Antifibrinolytic Therapy

To date, multiple systemic reviews, meta-analyses and randomized clinical trials, including thousands of patients, have failed to demonstrate an increased risk of thromboembolic events when TEA is used in primary TKA or THA, as outlined in Table 2.3. Based on the results of these studies, the risk remains theoretical. Perhaps the most convincing evidence comes from a systematic review published in 2009, showing no

significant difference in rates of reported thromboembolic events in 949 patients

receiving antifibrinolytic therapy as adjunctive therapy prior to TKA or THA[66]. Caution

must be taken when interpreting these studies; patient selection remains an important step

when considering the use of tranexamic acid. Although not always clearly stated, most

published series in TKA and THA exclude potential subjects with a medical history of

coagulopathy, cerebrovascular event(s), or any thromboembolic event. In some studies,

patients having undergone cardiac stenting, as well as females on long-term estrogen

replacement therapy have also been excluded from receiving TEA. Further evidence is

needed to supporting the administering of TEA in these higher-risk patient populations,

for any of the documented routes of administration.

Table 2.3: Systematic Reviews and Meta-Analyses Assessing Antifibrinolytics in Lower Extremity Total Joint Arthroplasty.

Procedure	Comparison	No. Studies	Blood Loss	Transfusion	Complications
Ho and Ismail (2003)[67]					
1° TKA 1° THA	1. IV TEA 2. Placebo	12	TEA < placebo	TEA < placebo	TEA = placebo
Cid and Lozano (2005)[68]					
1° TKA	1. IV TEA 2. Placebo	9	NR	TEA < placebo	NR
Gill and Rosenstein (2006)[69]					
1° TKA RevTKA 1° THA RevTHA	1. IV TEA + Apr 2. IV TEA 3. Apr 4. Placebo	13	All < placebo (intraoperative) All < placebo (total)	All = placebo	All = placebo
Zufferey et al (2006)[70]					
1° TKA RevTKA 1° THA RevTHA Spine Tumor	1. IV AFlytic 2. Placebo	23 Apr 20 TEA 2 EACA	NR	Apr < placebo TEA < placebo EACA = placebo	AFlytic = placebo
Kagoma et al (2009)[66]					
1° TKA 1° THA	1. IV AFlytics (Apr, TEA and EACA) 2. Placebo	29	AFlytic < placebo	AFlytic < placebo	AFlytic = placebo
Sukeik et al (2011)[71]					
1° THA	1. IV TEA 2. Placebo or other AFlytic	11	TEA < placebo (intra-operative)	TEA < placebo	TEA = placebo

Procedure	Comparison	No. Studies	Blood Loss	Transfusion	Complications
			TEA < placebo (postoperative)		
Gandhi et al (2013)[72]					
1° TKA 1° THA	1. TEA (IV, IA or Top) 2. Placebo	29 IV 3 IA 1 Top	TEA < placebo	TEA < placebo	TEA = placebo
Zhou et al (2013)[73]					
1° THA	1. IV TEA 2. Placebo	19	TEA < placebo (intraoperative) TEA < placebo (postoperative)	TEA < placebo	TEA = placebo

*EACA: Epsilon-Aminocaproic Acid. Apr: Aprotinin. IV: Intravenous. IA: Intra-Articular.
AFlytic: Antifibrinolytic (includes TEA, EACA, and Apr). NR: Not Reported.*

3 TeACH-R Trial Methodology

The purpose of our study is to compare the clinical efficacy of TEA given both intravenously prior to skin incision and topically at the time of arthrotomy closure during THA. A single-blinded, parallel group randomized controlled trial (RCT) forms the basis of our investigation. During the Study Initiation, Recruitment and Data Collection Phase, the study is colloquially termed the Tranexamic Acid Comparison in Hip Replacement (TeACH-R) Trial.

3.1 Clinical Trial Design

Well-designed randomized controlled trials provide sound Level I evidence for or against the use of a particular intervention, in accordance with the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence[74]. Our study design uses a parallel group design, with one treatment arm receiving intravenous TEA, the other receiving topical TEA. There is no placebo group in this trial; the active comparator is the intravenous tranexamic acid group, as this route of administration is considered the standard of care for primary THA at London Health Sciences Centre, University Hospital (LHSC-UH).

3.1.1 Ethics Board Approval

The Western University Health Science Research Ethics Board (HSREB#104559) and the Lawson Health Research Institute Clinical Impact Research Committee (CRIC#R-14-130) have approved the TeACH-R Trial for use of human participants in clinical research. Documentation of HSREB approval is provided in Appendix B. The clinical trial has also been registered into the public domain on clinicaltrials.gov (NCT#02056444).

3.1.2 Source of Funding

The TeACH-R Trial is supported by a Resident Research Grant (RRG) valued at $5000 Canadian Dollars, distributed as part of the Internal Research Fund from the Western

University Department of Surgery. No other sources of external funding were required to support the administrative or logistical needs of the study.

3.1.3 Randomization

Randomization assures that best efforts are made to equalize treatment groups with regards to demographic variables and expected prognosis. By allocating enrolled study participants to separate treatment groups, bias for treatment outcome is minimized. Inclusion and exclusion criteria help to define those patients screened for study inclusion by identifying factors that are known determinants of outcome. Minimizing bias related to unknown or uncontrollable determinants of outcome is corrected for by allocating to treatment groups on a random basis.

There are a number of ways to randomize effectively. Computer-generated random sequencing programs offer a straightforward and reliable method. Sealed opaque envelope concealment is also effective, and easy to administer. With the latter technique, however, there is the potential for error or investigator-driven allocation if envelopes are improperly sealed, or if the result of the allocation is visible through the envelope. We proceeded with sealed-envelope concealment, ensuring that tamper-proof manila envelopes were opened in succession.

In an attempt to keep even numbers between the treatment groups, a block randomization protocol was used. For every 20 participants enrolled into the study, 10 were to be randomized to the intravenous TEA group, and 10 to the topical TEA group. Randomization to receive either intravenous or topical TEA during primary THA occurred prior to the start of the procedure. As outlined in Section 3.2.3, verbal consent was obtained via telephone conversation with the potential participant prior to the operative date. Once verbal consent was confirmed, randomization to one of the two treatment arms proceeded.

3.1.4 Blinding

Blinding, as it relates to clinical trial research methodology, refers to the awareness of treatment group allocation for study participants. A study is single-blinded if either the

participant or investigator is unaware of treatment group allocation. A double-blinded study, on the other hand, implies that both the participant and investigator are blinded. The TeACH-R trial is blinded to patients only, as all outcome measures are objective in nature. TeACH-R investigators responsible for consent, randomization and data collection do not direct patient care. Patients may, however, be biased to disclose relevant medical information in the postoperative period if left unblinded. Willingness to disclose an adverse event could be influenced by patient perception, should he or she know which treatment group they have been allocated to. For example, a participant may feel that there is an increased risk of thrombotic events with the intravenous TEA; the threshold to seek investigations for swelling or leg pain might be lower than if the participant was not blinded to the treatment received. The investigators have designed the study to decrease this reporting bias; patients can only find out by which route they have received the drug after the final outpatient follow-up, at 3 months after total hip replacement. Data was unblinded at a specific time point after recruitment (April 1, 2014) in order to perform interim statistical analysis. All outcome measures are objective in nature, with no potential of introducing bias into the data collected as part of the TeACH-R study protocol. Only the primary author (R.P.N.) holds access to the data; consultant surgeons contributing to study development are not granted access to view, edit or input data pertaining to the TeACH-R trial.

3.2 Recruitment

The recruitment phase for the TeACH-R trial began in April 2014 and is ongoing. The process of approaching and enrolling potential participants is outlined below.

3.2.1 Eligibility

The goal of this study is to capture primary total hip arthroplasty (THA) patients who would otherwise be receiving IV TEA as the standard of care at our institution. Inclusion criteria are meant to represent the typical patient proceeding to elective THA, and are listed in Table 3.1. Five of seven fellowship-trained arthroplasty surgeons at LHSC-UH participated in the study. Two surgeons abstained from study participation. One surgeon cited an unwillingness to administer any intra-articular agent during arthroplasty, while

the other utilizes a direct anterior approach for primary THA in patients with a body mass index (BMI) below 40 kg/m^2. Above this level, it was felt by this surgeon that the risk of postoperative wound problems was significant enough to warrant a direct lateral approach, where the incision line is away from the inguinal crease and abdominal pannus (personal correspondence). As this is not the surgeon's preferred approach to a primary THA, and that the baseline risk of complications in morbidly obese patients is significantly different than the population targeted with the proposed intervention[75], the investigators decided to exclude this surgeon's patients from TeACH-R study participation. Patients from these two consultants were not screened nor contacted by the TeACH-R investigators.

Table 3.1: TeACH-R Trial Inclusion Criteria.

1.	Primary total hip arthroplasty.
2.	Primary diagnosis of osteoarthritis, rheumatoid arthritis, or avascular necrosis affecting the operative hip joint.
3.	Age over 18 years.
4.	Plan for cementless hip implant system.
5.	Plan for modified direct lateral (Hardinge) approach, in the lateral decubitus position.
6.	Medically fit for elective surgery.
7.	Consent obtained for blood product administration.
8.	Ability to read and write in the English language.

If the criteria for TeACH-R study inclusion were met at this stage, the subject was considered a potential study participant, but could still be disqualified from study participation if he or she met any of the exclusion criteria listed in

Table 3.2. Exclusion criteria are focused on THA patients with additional risk factors for venous thrombotic events (VTE) as well as those with atypical diagnoses requiring THA. Patients at higher risk of VTE require thorough medical review prior to treatment with TEA, and do not represent the population targeted with this intervention. The therapeutic safety of TEA has not been thoroughly studied in patients at moderate- and high-risk; investigators have expressed concern in administering a clot-stabilizing drug to a high-risk patient undergoing a moderate- to high-risk procedure.

Table 3.2: TeACH-R Trial Exclusion Criteria.

1.	Primary total hip arthroplasty for the treatment of acute hip fracture.
2.	Primary diagnosis of post-traumatic osteoarthritis (including those with or without the need for removal of hardware prior to prosthetic implantation), or Charcot arthropathy in the operative hip joint.
3.	History of developmental dysplasia of the hip, slipped capital femoral epiphysis or Legg-Calvé-Perthes disease in the operative joint.
4.	Simultaneous bilateral primary THA.
5.	History of VTE in last 12 Months, for any reason.
6.	Lifelong anticoagulation prescribed or recommended for prior VTE.
7.	Concurrent active malignancy receiving chemo- or radiation therapy, or having received said therapy in the past 12 months.
8.	Mechanical cardiac valve requiring lifelong therapeutic anticoagulation.
9.	Drug-eluting cardiac stenting within the previous two years to treat coronary artery disease, with ongoing clopidogrel (Plavix) therapy.
10.	Documented coagulopathy, blood dyscrasia, or hematologic condition/malignancy.
11.	Documented diagnosis of hemochromatosis with elevations of hemoglobin above normal range (> 170 mg/dL), or requiring recurrent phlebotomy.
12.	Documented allergy to TEA.
13.	Preoperative autologous blood donation.
14.	Inability to attend scheduled follow-up appointments with the treating surgeon.
15.	Participation in a concurrent research study at the time of THA

Atypical presentation of degenerative hip disease as a consequence of disease processes such as developmental dysplasia of the hip (DDH), slipped capital femoral epiphysis (SCFE) and Legg-Calvé-Perthes disease (LCPD) are relatively rare. These pathologies tend to affect patients decades earlier than the typical sufferer of OA, given the manifestation of these conditions in childhood. Younger patients typically have competent hematopoietic and cardiovascular systems, and are typically better able to withstand the physiologic stress of major orthopaedic surgery compared to those of advanced age. However, this population may still glean benefit from a reduced risk of transfusion, especially in young females of childbearing age. The risk of development of autoantibodies possibly affecting future pregnancies is not insignificant in a young female after transfusion of blood products. However, the surgical procedure is often more involved than the standard THA, due to the longstanding nature of hip pathology with consequent anatomic abnormalities. In LCPD and SCFE, altered femoral head shape can lead to significant bone loss in and around the acetabulum. Surgeons incorporate structural bone grafts or metallic augments to support the implanted

acetabular shell given these bony deficiencies. Dealing with these bone defects adds time and labor to the standard THA. Hip dysplasia surgery may also require femoral shortening osteotomies in severe deformities to bring the hip center back to its anatomic position. These accessory steps within the procedure, not commonly performed in elective primary THA, prolong the time of surgery and increase blood loss. Moreover, additional manipulation of the operative extremity can increase the risk of clot formation due to repeated endovascular disruption. From a research methodology perspective, these factors are significant confounders, and have the potential to skew the data in an unfavorable manner. Although TEA may be of benefit, patients affected by these disease processes are not representative of the typical arthroplasty patient population. Given the lack of evidence supporting the use of TEA in patients with these primary diagnoses, patients with DDH, LCPD and SCFE in the operative extremity were excluded from the TeACH-R study.

Adult avascular necrosis (AVN) of the hip represents a different etiological entity than those mentioned above. Subjects with AVN as a primary diagnosis are eligible for study inclusion. AVN often results in irreversible femoral head collapse due to weakening of subchondral bone. Clinical presentation is variable. Altered joint motion due to the misshapen femoral head results in progressive degenerative changes within the hip joint. Often, clinical deterioration is rapid compared to OA or inflammatory arthritis, and symptomatology dictates the need for THA early in the natural history of this aggressive disease. Femoral or acetabular bone loss is infrequently seen in AVN; therefore the surgical procedure is typically similar to a standard cementless primary THA for primary OA. For this reason, TEA can still be of benefit in patients affected by this disorder.

Subjects with inflammatory arthropathy as a primary diagnosis are eligible for study inclusion. Rheumatoid arthritis (RA) is a common form of inflammatory arthropathy. The inflammatory process within the hip joint results in both erosive and degenerative changes heralding the need for THA. The patient with inflammatory arthropathy often has concurrent alterations in their hematologic profile, with decreased hematopoietic potential. Commonly, these patients are anemic preoperatively and have pre-formed autoantibodies as a result of immunologic dysregulation. The prevalence of anemia in

patients with RA is thought to be anywhere from 30 to 60 percent. In combination, both iron-deficiency anemia from longstanding anti-inflammatory use and anemia of chronic disease due to autoimmune attack on hematopoietic cells within the bone marrow contribute to the increased prevalence of anemia in RA patients[76]. Avoidance of transfusion in the rheumatoid population is therefore paramount; procuring an allogeneic match is often difficult, costly, time-consuming, and exposure to repeated transfusion increases the risk of forming additional allo-antibodies[77]. The benefits of administering TEA far outweigh the risks for the patient with inflammatory arthropathy needing THA for the management of symptomatic hip disease.

3.2.2 The Preoperative Medical Evaluation

Once the determination has been made to proceed with surgery to replace the degenerative hip joint, all arthroplasty patients at LHSC-UH undergo a thorough medical review in the Pre-Admission Clinic (PAC). This is in addition to the orthopaedic-specific medical history taken at the time of initial consultation with the treating surgeon. At this PAC visit, Orthopaedic Nurse Practitioners (ONP) are tasked with performing a thorough review of systems, documenting all preoperative medications, and placing day-of-procedure orders, to be implemented as the patient arrives to the Surgical Preparation Unit on the day of the elective procedure. Specialist Internal Medicine or Anaesthesia consultations are completed during the PAC visit, should the need arise based on medical conditions identified during the orthopaedic consultation or ONP medical review.

Timing of the PAC visit is meant to provide up-to-date medical information to all involved in the care of the arthroplasty patient. The planned date of the surgical procedure is known, and the PAC appointment is scheduled anywhere from 1 week to 3 months prior to the surgical date. This allows for enough time preoperatively to order urgent investigations, if necessary, and to advise on medication profile alterations, without changing the date of surgery. Updated blood work, including a complete blood count (CBC), is drawn if the planned procedure is more than 3 months from the date of the most recent available values. The CBC includes the hemoglobin (Hgb) and hematocrit level (Hct); values nearest to the operative date and time are used as baseline for the calculation of perioperative blood loss in this study.

The order for TEA is placed electronically at the PAC visit, along with other day-of-procedure orders. The ONP is responsible for assessing the need and eligibility for intraoperative TEA administration, based on the Medical Directive set by the Perioperative Blood Conservation Program (PBCP). The latter outlines the circumstances where TEA can be given safely to patients undergoing both THA and TKA (See Appendix D). The majority of arthroplasty patients fall into one of two categories: (1) no concern exists with regards to TEA administration, or (2) an absolute contraindication exists within the patient's medical profile. In the first scenario, the ONP places the order after the PAC encounter is completed. In the latter scenario, no TEA order is placed on the chart.

If any element of the patient medical history raises concern with regards to the safety of administration of TEA, further review by the PBCP is indicated. The PBCP is composed of a number of specialist physicians, including hematologists, surgeons and anaesthesiologists, whose main responsibility is the creation of policies to optimize the use of cost-effective and safe blood conservation protocols in the perioperative setting. On a case-by-case basis, three individuals work in unison to determine eligibility for TEA administration: a supervising physician with subspecialty interest in perioperative medicine and blood conservation (the Director), working in direct consultation with two PBCP nurse practitioners. Final determination of perioperative TEA administration in equivocal cases comes after the PCBP Director performs a thorough medical review and risk-benefit analysis. This process is unaffected by the TeACH-R protocol.

3.2.3 Informed Consent

Informed consent for study participation was obtained pre-operatively for all study participants. The process of informed consent was undertaken as per Good Clinical Practice (GCP) standards. Possible study participants were identified by thorough review of surgical lists. A chart review was undertaken for subjects meeting TeACH-R study inclusion criteria. If no exclusion criteria were identified based on the available information contained within the subject's chart, contact was made prior to the day of the procedure, either by telephone or at the PAC visit. Usually, the study participant had completed the PAC appointment with day-of-procedure orders visible on the electronic

chart before being contacted by a member of the research team. This process enabled the research team to select study participants whom had already been ordered TEA by either the ONP or PBCP.

Verbal consent was obtained at the time of initial patient contact. Written informed consent was then obtained on the morning of surgery, where the study objectives and protocol were reviewed, and all questions answered. A copy of the written consent form is provided in Appendix C. Subjects were deemed to be enrolled in the study only after written informed consent was signed and dated; the option to decline participation was allowed up until this point. Should a patient enrolled in the topical TEA treatment arm decline participation preoperatively, he or she would still receive the standard of care, intravenous TEA, prior to skin incision. Consent can be retracted postoperatively, at the participant's request. Although he or she would have received treatment based on randomized allocation to a treatment arm, participant data is not to be included as part of the final analysis.

Signed original consent forms are kept in a locked room in a secure facility at University Hospital. The Western HSREB requires that these consent forms be maintained for ten years after completion of the enrollment phase of the TeACH-R study. A copy of the signed consent form was provided to all study participants at the time of formal study enrollment.

3.3 Treatment Arms

3.3.1 Intravenous Tranexamic Acid

At LHSC-UH, intravenous TEA is given to all patients undergoing primary THA so long as a particular patient does not have a contraindication to TEA administration. This is considered standard of care for both TKA and THA. Preparation of the medication is done the night prior to the procedure, by the Inpatient Pharmacist, with a weight-based dose of 20 mg/kg TEA mixed in a 50 mL bag of 0.9% sodium chloride. This is refrigerated overnight at 4° Celsius, sent to the Surgical Preparation Unit on the morning

of surgery and appended to the patient's chart (see Figure 3.1). The preparation travels with the patient to the Operating Room (OR), where it is administered 10 minutes prior to skin incision for THA via intravenous injection by the anaesthesiologist assigned to the OR on that particular day. For the purposes of this study, intravenous TEA is considered active five minutes after completion of the infusion, as the drug has had enough time to redistribute into the joint space.
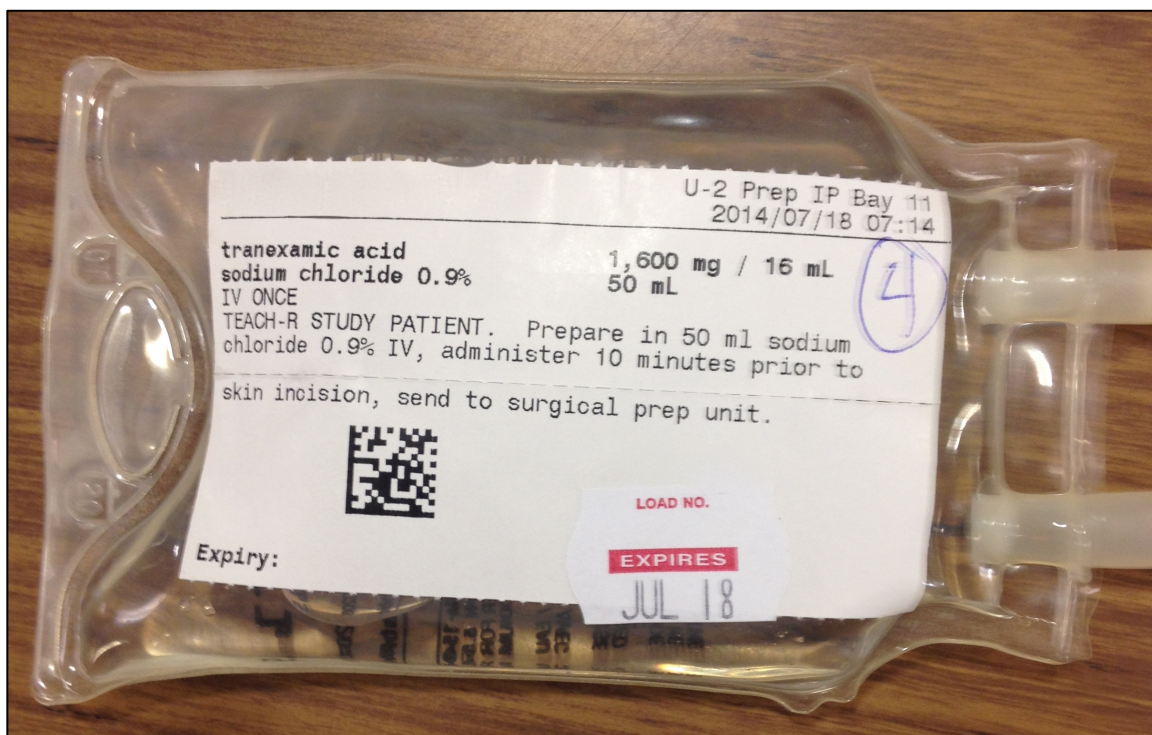
Figure 3.1: Intravenous Tranexamic Acid Preparation.

As discussed in Chapter 2, both single-dose and serial dosing TEA regimens are prevalent in the literature. Logistical barriers related to patient transport, equipment, and nursing exist in the perioperative setting that can impair the implementation of a reliable multi-dose or TEA-infusion protocol. We elected to use a single-dose regimen of 20 mg/kg given immediately prior to skin incision. This protocol is the standard of care currently in use at LHSC-UH for THA. This has proven effective at our institution in reducing blood loss without a concomitant rise in thromboembolic events post-THA[46].

3.3.2 Topical Tranexamic Acid

Topical TEA is prepared in a similar fashion to the intra-articular preparation used in TKA. Like the intravenous TEA group, the Inpatient Pharmacist prepares the solution the night prior to the procedure. However, in the topical TEA group, a standardized solution of 1.5 grams in a 50 mL solution of 0.9% sodium chloride is prepared. The solution is contained within a sterile syringe sent to the Surgical Preparation Area, and subsequently to the OR with the study participant (see Figure 3.2). For subjects allocated to this treatment arm, no intravenous TEA is administered prior to skin incision. Instead, the solution is applied to the joint area intraoperatively by the treating surgeon. This takes place with the final implants *in situ* after final reduction of the prosthetic components. The entirety of the 50 mL TEA solution is applied to the joint prior to closure of the gluteus minimus and capsular tissue layers. The solution bathes the hip joint and surrounding tissues for a minimum of 5 minutes. Closure of the arthrotomy can continue during this waiting period, provided the solution is not suctioned away.

Figure 3.2: Topical Tranexamic Acid Preparation.

Timing and dosage are important considerations when TEA is administered via the topical route. Optimal timing of administration must parallel the timing of expected increases in blood loss. In THA, the majority of intra-articular blood loss emanates from

cancellous bone at the sites of the femoral neck osteotomy and acetabular reaming. This continues postoperatively until local hemostasis is achieved. We elected to target reductions in perioperative blood loss by infiltrating TEA after the intramedullary femoral canal has been filled with the stem of the press-fit femoral implant, and the acetabular cup sealed with the press-fit shell. In this fashion, we target sites of continued postoperative bleeding not amenable to electrocautery or ligation. This corresponds primarily to the exposed cancellous bone of the proximal femoral shaft, where TEA can act to inhibit the local fibrinolytic process postoperatively. In a recent study, Konig et al infiltrated 3 grams of TEA at three separate time points intraoperatively with good clinical outcomes with regards to blood loss[55]. In principle, this represents a useful strategy to maintain intra-articular does of TEA from the start through to the end of the operation. However, the investigators and arthroplasty surgeons felt the additional doses would result in intraoperative time delays due to the mandatory waiting period after TEA infiltration, potentially increasing the risk of infection. A single-dose regimen targeting the predominant source of blood loss was adopted for the purposes of this study.

Dosage of topical TEA was also an important consideration in the development of this study. There is little available evidence to guide the optimal dosing protocol for topical TEA administration in THA. However, to reiterate the aforementioned study by Wong et al, a 1.5 gram topical dose of TEA was shown to be effective in reducing blood loss when administered during TKA, with a clinically favorable systemic absorption profile[39]. Using this data, we chose to proceed with the identical dosing strategy for TeACH-R study participants undergoing primary THA. As surgical drains are no longer standard practice amongst the arthroplasty surgeons at our institution for THA, serial dosing of topical or intra-articular agents is not possible in the postoperative period.

3.4 Surgical Considerations

3.4.1 Operative Technique

A thorough description of key principles and approaches for THA is available in Section 1.2.1.1. The standard operative procedure for a primary cementless THA has been

defined for the purposes of this study. The modified direct lateral (Hardinge) approach, using a surgical incision based over the greater trochanter, was used for all study subjects. The gluteus minimus and capsular tissue layers were incised as one layer. The capsule was not excised following the arthrotomy. No restrictions were defined regarding the sequence of femoral and acetabular preparation, trialing of expected components, or prosthetic implantation. No surgical drains were placed intraoperatively. All patients received the standard weight-based dose of intravenous antibiotics within 30 minutes of skin incision. Typically, cefazolin is the antibiotic of choice. In cases of severe allergy or colonization with methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin and/or clindamycin are either substituted or added to the preoperative regimen. To the best of the author's knowledge, there are no known drug interactions between TEA and any of these intravenous antibiotics.

3.4.2 Prosthetic Components

When it comes to primary hip prostheses, a variety of implants are used at LHSC-UH. As per the TeACH-R protocol, choice of final prosthesis and bearing surface is at the discretion of the treating surgeon, as long as cementless fixation is used on for both the femoral stem and acetabular shell. If the latter criterion is not met, the patient is excluded from the study. This situation arises most commonly when there is concern of diminished bone density, identified intraoperatively, where cemented implants are thought to provide improved stability in the setting of poor osteo-integrative potential. The use of adjuvant screw placement through the acetabular component was also left to the discretion of the treating surgeon. Participants requiring acetabular screw placement as an added measure of stability were not excluded from the final analysis. Because placement of acetabular screws tends to increase operative time and increases the risk of bleeding, screw fixation was noted in the final analysis as a demographic variable.

3.5 Postoperative Care of the Arthroplasty Patient

3.5.1 Inpatient Care After Elective Primary Total Hip Arthroplasty

All patients undergoing total hip arthroplasty follow a standard postoperative pathway. The patient is transferred from the OR to the Post-Anaesthetic Care Unit (PACU) for close monitoring after completion of the period of anaesthesia. While in the PACU, the treating anaesthesiologist manages multi-modal analgesia protocols as well as any acute medical issues. A plain film radiograph of the pelvis is taken in the PACU shortly after arrival in order to assess the position of the implanted components and to rule out prosthetic dislocation or unidentified intraoperative fracture. Occasionally, a CBC is drawn in the PACU in cases in which there has been an unusual amount of bleeding intra-operatively.

Once the patient is deemed medically stable, he or she is transferred to the orthopaedic floor for continued rehabilitation and convalescence. On the inpatient orthopaedic floor, the focus of treatment is on early mobilization in order to reduce the incidence of postoperative complications. The surgical team rounds on each arthroplasty patient a minimum of once per day, monitoring for complications and tracking progress with mobilization. Daily blood work is routinely drawn the first two mornings after the day of surgery. Standard postoperative blood work consists of a basic hematology, coagulation and chemistry panel: CBC, electrolytes (sodium, chloride, potassium, bicarbonate and random glucose), blood urea nitrogen (BUN), creatinine (Cr), International Normalized Ratio (INR) and partial thromboplastin time (PTT). Supplementary investigations are dependent on clinical suspicion of postoperative pathology, or for monitoring of known medical conditions, drug levels, or therapeutic targets. This study does not alter the usual sequence of postoperative investigations. There is no additional screening or testing mandated by the TeACH-R study protocol.

Throughout the inpatient stay, there is a gradual increase in activity level, with the treating surgeon ultimately dictating weight-bearing restrictions based on personal preference and intraoperative findings. Implementation of hip precautions after surgery is standardized as per the pathway for THA postoperative care at LHSC-UH. Patients are

advised against hip flexion past 90° and excessive internal or external rotation of the thigh in order to prevent prosthetic dislocation. Given these restrictions, a gait aid is usually required for the first 6 weeks postoperatively, which is started in hospital on postoperative day 1. Physio- and occupational therapists see arthroplasty patients in hospital and provide daily education and assistance, enabling progression of mobility in preparation for a safe discharge from hospital. Readiness for discharge is a multi-faceted process with influence from various members of the interdisciplinary care team, where significant emphasis is placed on the patient's perception of ability to cope at home, support systems available to help in recovery, and general medical condition. Typically, patients are ready for discharge on postoperative day two or three following primary lower extremity arthroplasty. The usual discharge prescription consists of pain medication(s) and a thromboprophylactic agent to be taken on a routine basis once at their discharge destination.

3.5.2 Thromboembolic Prophylaxis after Primary Total Hip Arthroplasty

Major orthopaedic surgery, which includes THA, is a known risk factor for the formation of lower extremity clot. A deep vein thrombus (DVT), or blood clot, forms due to a combination of factors related to Virchow's triad of vascular thrombosis: endothelial injury, hypercoagulability and vascular stasis[78]. First, endovascular damage results from manipulation of the operative leg. Second, the release of procoagulant factors during bone preparation results in a hypercoagulable state that can persist in the postoperative period[79, 80]. Third, relative immobility during the convalescence phase promotes clot propagation due to venous stasis. If a clot increases to the point of impeding proper venous outflow in the affected limb, leg pain and diffuse unilateral swelling ensue, usually in the operative extremity.

Doppler ultrasonography of the lower extremity leg veins is the most commonly used method of providing a definitive diagnosis, showing poor compressibility of veins having a DVT. Pulmonary emboli (PE), on the other hand, are embolic phenomena. A clot in the operative (or non-operative) extremity dislodges from its endovascular source and subsequently travels through the inferior vena cava, through the right atrium and ventricle

past the tricuspid and pulmonic valves, to eventually lodge in the smaller arteries of the lung. The latter can have a variable presentation in the postoperative period. Chest pains, shortness of breath, supplemental oxygen dependence, and/or unremitting tachycardia (in the absence of any other clinical explanation) are clinical scenarios that can herald the onset of thrombus migration to the lungs. Suspicion for thromboembolic events must be high after primary or revision THA because there is a risk of mortality associated with an unrecognized embolism. Diagnosis is confirmed with either a ventilation-perfusion scan or computerized tomography of the thorax with concomitant pulmonary arterial and venous angiography. Generally, a low threshold exists for investigating a potential clot.

Although many promote screening for a lower extremity thrombus after arthroplasty, high clinical vigilance and early investigation remains the standard of care in this patient population. Not all clots are symptomatic, nor do all clots require full anticoagulant therapy. The rate of symptomatic or fatal emboli remains unaffected by the presence of a radiographic DVT screening protocol, hence it is not recommended by the American College of Chest Physicians in their most recent guideline statement[17]. Moreover, there is currently no evidence to support an increased risk of thromboembolism in patients receiving TEA during TKA or THA[66, 72]. In keeping with the standard of care at LHSC, routine radiographic screening with duplex ultrasonography is not part of the TeACH-R trial protocol.

Postoperative thromboprophylaxis remains part of the postoperative care pathway after primary total hip arthroplasty at LHSC-UH. Many agents, including unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), vitamin K antagonists, factor Xa inhibitors (FXaI) and direct thrombin inhibitors (DTI) are effective in decreasing thromboembolic risk using prophylactic dosing regimens[17]. The TeACH-R study protocol does not discern which thromboprophylactic agent is used, so long as the study subject is on a prophylactic dose postoperatively. Prior to TeACH-R study initiation, the group of arthroplasty surgeons at LHSC completed a thorough review of the current evidence on thromboembolic prophylaxis after primary total hip arthroplasty. The group of surgeons using the modified Hardinge approach for THA universally adopted oral rivaroxaban 10 mg daily, given in the morning starting postoperative day 1 and

continuing for 30 days postoperatively. Rivaroxaban is a Factor Xa inhibitor growing in popularity as a result of well-documented clinical efficacy as a thromboprophylactic agent, with the ease of once-daily oral administration[20]. The agreed-upon regimen was deemed to be safe, effective, and better tolerated by patients compared to subcutaneous LMWH, which had been the predominant agent used in the past.

The thromboprophylaxis regimen at LHSC-UH uses chemical thromboprophylaxis alone, without the addition of external compression devices. Adding intermittent compression devices, foot pumps and/or compression stockings is not the standard of practice, as these are deemed to be a constant source of patient discomfort, and are a significant impediment to mobility during the in-hospital stay. The benefits of early mobilization free of any lower extremity device outweigh the benefit of these external devices. Implantable inferior vena cava filters are not used for prophylaxis due to the invasive nature of the procedure and marginal clinical benefit.

Data pertaining to which thromboprophylaxic agent a TeACH-R participant received at time of discharge is recorded as part of the study. Of note, a separate clinical trial comparing two DVT prophylaxis protocols combining rivaroxaban and acetylsalicylic acid after elective primary THA (the EPCAT-II Study) was underway at LHSC-UH at the same time as the TeACH-R Trial. Because of the possible influence of this latter study on rates of DVT and PE, any patient enrolled in EPCAT-II was excluded from TeACH-R study participation.

3.5.3 Transfusion Protocol

As discussed in Section 1.4.2, strong evidence supports limiting transfusion of packed red blood cells (pRBC) in the acute care setting in order to decrease morbidity and mortality. Although there are no studies specific to THA, there is definitive evidence stemming from two prospective randomized controlled trials, one in critically ill patients patients[22], and the other in patients having received hip fracture surgery[27]. As a result, a restrictive transfusion protocol is the standard of care for the arthroplasty service at LHSC-UH. TeACH-R study investigators responsible for data collection and analysis, although not

directly involved in the postoperative treatment of a study subject, support this

transfusion strategy, as outlined in Figure 3.3.
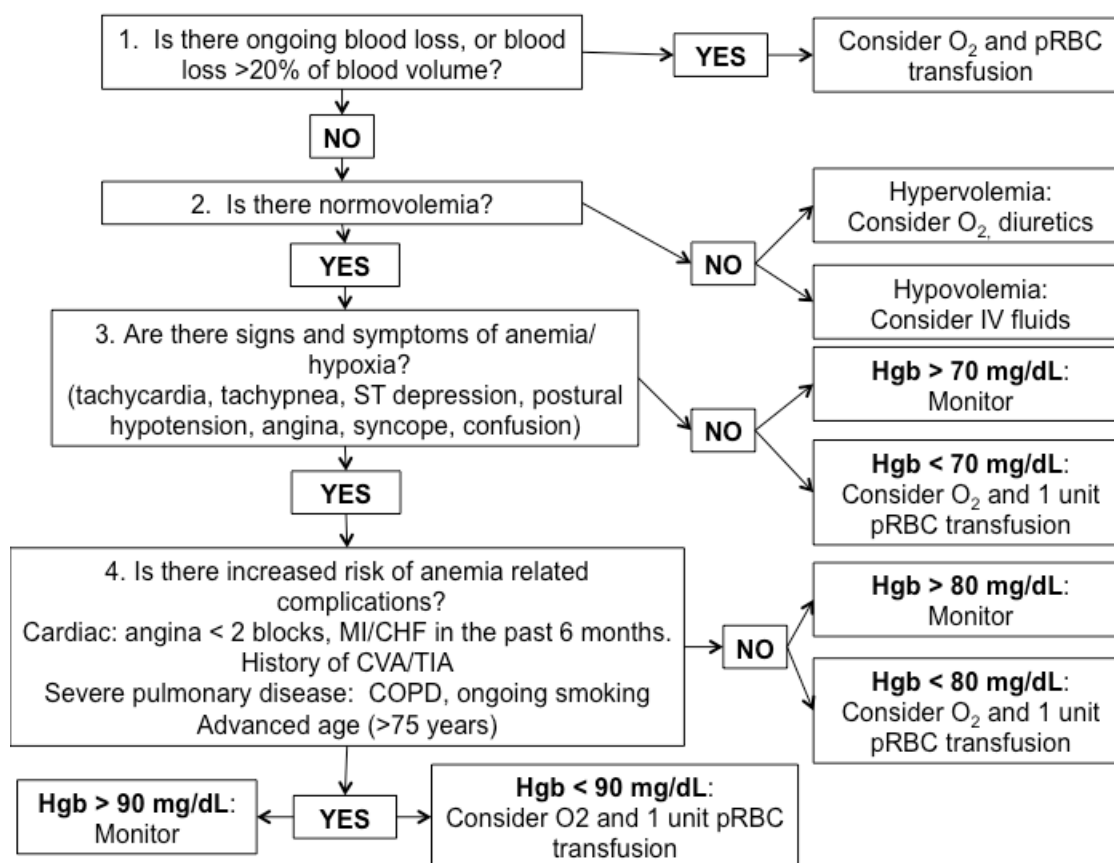
Figure 3.3: Restrictive Transfusion Algorithm for Postoperative Anemia in Arthroplasty Patients at London Health Sciences Center, University Hospital.

Violations of the restrictive transfusion strategy were recorded. If a transfusion of

pRBCs was initiated, all clinical notes from the inpatient stay were reviewed in an

attempt to find a documented reason for transfusion. The number of units administered

was recorded as per the TeACH-R trial protocol.

Preoperative autologous blood donation (PAD) and postoperative reinfusion (PRI) of

drained blood after arthroplasty, although not used at LHSC-UH, is still commonplace in

certain centers. Issues in incorporation of these modalities as perioperative blood

conservation adjuncts are discussed in Section 1.4.3. Subjects are excluded from the TeACH-R trial if these modalities are used in the perioperative period.

3.5.4 Outpatient Follow-Up

At LHSC-UH, patients undergoing THA have scheduled follow-up with the treating surgeon at the 6-week, 3-month and 1-year mark. Depending on surgeon preference, a patient may also be seen at the 2-week mark for a wound check. At time of discharge from hospital, the first two clinic appointments are coordinated with the surgeon's office. Patients are given strict instruction to contact a member of the surgical team should there be any concern related to their surgery in the early postoperative period. During business hours, patients can contact the surgeon's office directly; after discussion with a member of the surgical team, the decision is made to either see the patient in clinic or if urgent, to proceed to the Emergency Department at University Hospital for further evaluation. Outside of usual business hours, patients have direct telephone access to the on-call orthopaedic resident at University Hospital. This has traditionally been a well-developed process for identifying, treating and documenting complications locally.

TeACH-R study participants are followed for 3 months after surgery. Contact is made with the patient at 2 weeks, 6 weeks and 3 months postoperatively, usually in person at the time of outpatient follow-up, where a member of the research team assesses for the presence of any postoperative complications. If in-person contact is not possible, completion of the questionnaire is via telephone correspondence by a member of the research team. All clinical notes are reviewed, also with the goal of identifying any complications related to the new intervention that are not disclosed by the subject. The TeACH-R study protocol does not mandate any repeat blood work or additional investigations at outpatient clinic follow-up appointments. Loss to follow-up is noted in the final analysis.

3.6 Data Collection

Data collection began once the patient has been formally enrolled into the study, has been randomized to one of the two treatment arms, and continues his or her postoperative course up to the three-month follow-up appointment with the treating surgeon. All data is collected prospectively. At LHSC-UH most of the available data is contained on the patient's electronic chart (PowerChart, Cerner Corporation, Kansas City, MO), although at times reference to the participant's paper chart is required for further information. Data collected is devoid of identifiable patient information, with representative study identification numbers assigned to all TeACH-R trial participants. All collected data is contained within study binders stored in a secure location in a locked office, accessible only to TeACH-R trial investigators. A password-protected Microsoft Office Excel spreadsheet (Microsoft Corporation, Redmond, WA) also contains de-identified participant data for analysis. This is stored on a secure server (the P: drive) within the LHSC computer system, accessible only via secure user login. In this fashion, confidentiality of patient information is ensured throughout the data collection phase. The author (R.P.N.) collected all data relevant to the TeACH-R Trial.

3.6.1 Demographics

The purpose of collecting demographic data in a prospective randomized controlled trial is to ensure that both treatment groups are similar at baseline after randomization. With an appropriate sample size and similar profiles, potential between-group differences in the dependent variable(s) are related to the variable controlled by the study itself (independent variable); in this study, this would be administration of either intravenous or topical TEA. All demographic variables collected as part of the TeACH-R study are listed in Table 3.3. In addition to basic demographic variables, a number of variables pertaining to the surgical procedure and comorbidities were also collected.

Table 3.3: TeACH-R Demographic Variables.

Patient-Specific Demographic Data
Age (at Time of Surgery)
Gender
Height (cm)
Weight (kg)

Body Mass Index (BMI; kg/m^2)
Body Surface Area (BSA; m^2)
Primary Diagnosis (OA, RA, AVN)
Preoperative Anemia (Hgb<120 in females, Hgb<130 in males)
Medical Comorbidities (Charlson Age-Comorbidity Index)
Previous Myocardial Infarction
Congestive Heart Failure
Peripheral Vascular Disease
Cerebrovascular Disease (Stroke, Transient Ischemia Attack)
Dementia
Chronic Obstructive Pulmonary Disease
Connective Tissue Disease
Peptic Ulcer Disease
Diabetes Mellitus (with and without End-Organ Damage)
Moderate to Severe Chronic Kidney Disease
Hemiplegia
Leukemia
Malignant Lymphoma
Solid Tumour
Liver Disease (Mild, Moderate or Severe)
Acquired Immunodeficiency Syndrome (AIDS)
Intraoperative Variables
Duration of Procedure
Type of Anaesthesia (General or Regional with Sedation)
American Society of Anaesthesiologists (ASA) Physical Status Score
Acetabular Screw Placement

3.6.1.1   Combined Charlson Age-Comorbidity Index

The presence of medical comorbidities is known to alter the risk of postoperative complications after THA. Therefore, assessing the aggregate baseline risk level for each treatment group is essential. As de Groot stated in his 2003 article, "comorbidity can either act as a confounder, threatening the internal validity, or as an effect modifier, threatening the internal and external validity of the study."[81] The difficulty in assessing preoperative risk based on comorbidities lies in filtering through the variety of medical diagnoses of relevance, as well as the numerous methods at our disposal to assess preoperative risk.

The Charlson Comorbidity Index, initially described in 1987, is a weighted scale inclusive of 19 disease processes, listed in Table 3.3, that has proven to be a useful tool in prognosticating outcomes[82]. It is also user-friendly, comprehensive, and most

importantly, predictive. The structure of the index allows straightforward assessment of risk factors for perioperative complications, in addition to prognosticating long-term morbidity and mortality. It is validated for use in arthroplasty, as it has shown excellent validity for mortality, disability, hospital readmission and length of stay[81]. When a combined age-comorbidity score is used, the impact of increasing comorbidity is easy to understand, as per Gold in his 1994 article: "the estimated relative risk of death from an increase of one in the comorbidity score proved approximately equal to that from an additional decade of age."[83] After a thorough review of the available methods, the TeACH-R study investigators felt the combined age-comorbidity score would provide the more reliable measure of assessing known preoperative comorbidities for the purpose of baseline comparison between both of the treatment arms.

3.6.1.2   Intraoperative Variables

When designing a procedure-related RCT, analysis of intraoperative variables is also critical, as there can be subtle differences in process for two patients receiving the same operation. Intraoperative proceedings, and how they compare to the standard operating procedure, are difficult to assess given the significant heterogeneity in patient anatomy, physiology and surgeon preference. Thankfully, there is available data contained within the Intraoperative Record, Anaesthetic Record and Operative Report that allows for some standardization between both treatment arms.

For every patient proceeding to the OR, the attending anaesthesiologist, a specialist in perioperative medicine, places significant importance on a through review of medical conditions prior to induction of anaesthesia. The American Society of Anaesthesiologists (ASA) Physical Status Score is still commonly used as a standard measure of operative risk, despite concerns surrounding scientific precision and limited inter-observer reliability[84]. The classification system is presented in Table 3.4. The attending anaesthesiologist states and records the ASA Score at the beginning of every case, as part of the World Health Organization-mandated surgical debriefing. This is also recorded as per the TeACH-R Trial protocol. Although less robust than the Charlson Age-Comorbidity Index, it provides an added measure of assessing preoperative risk based on

comorbidity and is helpful in assessing for any baseline between-group differences, in the eyes of the anesthesiologist.

Table 3.4: ASA Physical Status Classification System.

Class 1	A normally healthy patient.
Class 2	A patient with mild systemic disease.
Class 3	A patient with severe systemic disease.
Class 4	A patient with severe systemic disease that is a constant threat to life.
Class 5	A moribund patient who is not expected to survive without the operation.
Class 6	A declared brain-dead patient whose organs are being removed for donor purposes.

The type of anaesthesia is also collected as part of the TeACH-R data set. Although beyond the scope of this study, the influence of the type of anaesthesia, and its resultant effect on surgical outcome after TKA or THA, continues to be debated amongst anesthesiologists worldwide given a lack of recent high-powered clinical trials. Meta-analysis data does, however, suggest that regional anaesthesia decreases operating time and the risk of postoperative thromboembolism when compared to general anaesthesia in THA[85]. There is also a significant effect on surgical blood loss, with decreased transfusion requirements reported for THAs done under spinal anaesthesia[86]. In general, the TeACH-R protocol places few restrictions on the intraoperative process. No patient was included or excluded from the study based on whether they received general or regional anaesthesia, but this data was recorded for every study participant.

From the surgical standpoint, increased surgical time leads to increased blood loss if a constant rate of loss is maintained for the duration of the procedure. The precise start and end time of the procedure was also collected from the Intraoperative Record as part of the TeACH-R study protocol. The need for acetabular screw fixation, sometimes required to add stability to the acetabular implant after reaming in poor-quality bone, is not expected to add significantly to perioperative blood loss as the screws are sealed within the implanted shell and threaded into the cortico-cancellous bone of the pelvis. These are placed at final implantation of the acetabular component. However, the risk of arterial or

venous injury potentially leading to hemorrhage and blood loss increases with faulty screw placement in an at-risk zone. The addition of this intraoperative step also increases operative time, although generally by a small amount. For these reasons, both variables were also recorded as baseline measures and potential statistical confounders.

3.6.2 Primary Outcome Measures

The benefit of introducing TEA into the usual blood conservation for a patient undergoing primary THA is to further decrease blood loss. The predominant risk of administering a clot-stabilizing agent during THA is the potential for increased rates of thromboembolic complications in the postoperative period. The primary and secondary outcomes measured by the TeACH-R trial attempt to encompass these risks and benefits by the most reliable means possible.

3.6.2.1   Change in Hemoglobin Levels (Delta-Hemoglobin)

The delta-hemoglobin (ΔHgb), defined for the purposes of the TeACH-R trial as the difference between the Hgb value nearest the date of surgery and the lowest measured postoperative Hgb, represents a main driver of clinical decision-making with regards to the need for transfusion for the control of postoperative blood loss. It represents one of two primary outcomes measures of the TeACH-R trial. Clinically, should clinical concern of acute hemorrhage exists, the first investigation ordered is often a CBC for the purposes of determining a Hgb level. The preoperative Hgb level, a prerequisite for any patient undergoing a major surgical intervention where a significant amount of blood loss is expected, is also an intuitive marker of underlying red blood cell mass. Decreases in postoperative Hgb level represent loss by one of two mechanisms: (1) external loss (hemorrhage) or (2) intrinsic red cell degradation (hemolysis). In the immediate postoperative setting, interpretation of Hgb levels is straightforward, requiring little calculation or analysis as loss of red cell mass is predictably due to continued extravasation of intravascular volume outside the vascular tree. Given the period of 120 days needed for a reticulocyte to mature into a functioning red blood cell, anemia due to lack of production of red blood cells is limited to chronic, rather than acute etiologies of blood loss.

Blood analysis for Hgb levels can be performed rapidly, enabling point-of-care decision-making in times of need. The classic clinical presentation of blood loss after THA is more gradual in onset, and the treatment consists of transfusion of pRBC as per the protocol outlined in Figure 3.3. Typically, a low Hgb level is discovered incidentally as part of the routine postoperative blood work. As explained in Section 3.5.1, postoperative blood work is available for the patient's in-hospital stay, which is used to calculate the ΔHgb in the TeACH-R trial. Unless there is concern for early postoperative infection, no further blood work is indicated once discharged from hospital.

The clinical utility of the Hgb level as a transfusion trigger is well documented. However, assessing surgical blood loss based on either isolated Hgb values, or the change in Hgb lacks precision. Commonly used as a surrogate marker of blood loss, it is important to note the various factors contribute to one isolated Hgb value drawn in the perioperative setting. One cannot accurately calculate the amount of blood lost using Hgb values alone, for a number of reasons. A falsely elevated Hgb level may result if bloodwork is drawn while there is continued bleeding. Dilution by crystalloid or colloid intravascular fluid administration can also alter the apparent red cell mass due to intra- and extravascular fluid shifts. Intraoperative irrigation and suctioning can also alter the systemic fluid balance, resulting in potential hemodilution. Specific to research methodology, however, there is great value in interpreting this measure as a scale when used as a comparator between groups, assuming that contribution of the other factors to Hgb levels remains constant amongst all participants. In this way, a significant difference in the ΔHgb can still indicate a difference in blood loss between groups. For this reason, the determination of ΔHgb in the perioperative setting remains an invaluable aid in the assessment of blood loss, which explains its use as a primary outcome in this prospective randomized controlled trial.

3.6.2.2   Calculated Red Blood Cell Loss

Determining the amount of surgical blood loss is a difficult endeavor, as the value that is truly of interest is actually the volume of red blood cells lost during and after the procedure. Red blood cells are the transporters of oxygen within the systemic circulation; it is the global increase in oxygen-carrying capacity that transfusion of red blood cell

aims to improve. Given that fluid status changes during and after surgery are dependent on the concentration of intra- and extracellular proteins, this can be challenging to predict and manage, let alone calculate accurately. There are a number of ways investigators have attempted to quantify perioperative blood loss in the referenced studies mentioned in previous chapters. Some have tried weighing intraoperative sponges, in combination with measuring the volume of intraoperative suctioning. Although commonly referenced as an acceptable measure of blood loss, the influence of fluid evaporation and the dilutional effect of intraoperative irrigation make this an imprecise measure of intraoperative red cell mass lost. In a similar light, drain output, with and without measurement of Hgb values within drain fluid, has been used to measure postoperative blood loss. These are imprecise measures as drain fluid emanating from the surgical wound is not the same whole blood lost as a result of surgical trauma. Inflammatory proteins and extracellular fluid infiltration into the surgical wound during the postoperative period can significantly influence the actual composition of the drained fluid. In addition to these biological factors, it is not possible to measure postoperative drained fluid if no drain is placed intra-operatively, as is common practice at LHSC-UH.

Pioneering work by Nadler and Gross[87, 88], and further work by Blecher[89, 90], allow researchers and to calculate the volume of red cell loss based on a comparison of estimated blood volume (EBV) pre- and postoperatively. This is based predominantly on hematocrit (Hct), defined as the percentage of whole blood that consists of pRBCs. Clinically, this is represented as a fraction of 1; for example, a Hct of 0.50 implies that 50% of whole blood is composed of red blood cells. Hematocrit takes into account dilution and protein composition, enabling calculation of red blood cell mass by multiplying the Hct with the EBV. The formula used for calculation of blood loss can be seen in Figure 3.4.

$$\text{Total RBC loss (mL)} =$$
$$\text{[Uncompensated RBC loss (mL)]}$$
$$+ \text{[Compensated RBC loss (mL)]}$$
$$\text{Uncompensated RBC loss (mL)} =$$
$$\text{[Initial RBC (mL)]} - \text{[Final RBC (mL)]}$$
$$\text{Compensated RBC loss} = \text{[Sum of}$$
$$\text{RBCs received from the various}$$
$$\text{sources of transfusion]}$$
$$\text{Initial RBC} = \text{[Estimated blood}$$
$$\text{volume (mL)]} \times \text{[Initial Hct level}$$
$$\text{(\%)]}$$
$$\text{Final RBC (mL)} = \text{[Estimated blood}$$
$$\text{volume (mL)]} \times \text{[Final Hct level (\%)]}$$

$$\text{Estimated blood volume (mL)} = \text{Women:}$$
$$\text{[Body surface area (m}^2\text{)]} \times 2430$$
$$\text{Men: [Body surface area (m}^2\text{)]} \times 2530$$
$$\text{Body surface area (m}^2\text{)} = 0.0235 \times$$
$$\text{[height (cm)]}^{0.42246} \times \text{[weight (kg)]}^{0.51456}$$
$$\text{And then, to obtain a result with blood}$$
$$\text{loss at a Hct level of 35 percent}$$
$$\text{Total blood loss (mL)} = \text{[Total RBC}$$
$$\text{loss (mL)]}/0.35.$$

Figure 3.4: Calculation of Perioperative Blood Loss. All blood loss referenced in the TeACH-R trial is based on whole blood, assuming Hct of 35 percent. Initial RBC calculated using the Hct and EBV from the preoperative blood draw closest to the date of surgery. Final RBC calculated using the lowest measured postoperative Hct. EBV is based on the most recent height and weight available on the patient's medical chart. (Adapted from Rosencher, N et al. *Transfusion* 2003; 43(4): 459-69)

Calculation of perioperative blood loss was performed for all patients enrolled in the study. As part of the PAC visit, all study participants had a recent height and weight available on the chart, enabling calculation of body surface area (BSA; in m^2). As part of the calculation in Figure 3.4, different formulas were used for both men and women, as per the formula for predicted blood volume in humans derived by Nadler et al[88]. The Hct value drawn closest to the operative date was used to calculate the initial RBC. The final RBC calculation used the lowest measured postoperative Hct level. A volume of 200 mL

per unit of pRBC transfused was used as standard for compensated RBC loss, when applicable.

3.6.3 Secondary Outcome Measures

Secondary outcome measures are defined by the investigators as areas of particular interest relating to, but not directly a part of the primary research question. They are termed secondary not due to lack of importance, but more because of statistical implications relating to power calculations. The relevance of findings for secondary outcome measures is subject to interpretation, as the power of a well-powered RCT is dependent on the degree of change of the primary outcome. However, important conclusions can be drawn from a study when clinically and statistically relevant outcomes are uncovered.

3.6.3.1   Transfusion Rate and Adherence to Transfusion Protocol

The goal of any blood conservation measure is to reduce the need for transfusion. As part of the TeACH-R protocol, we seek to uncover a difference in the rate of transfusion between groups. However, the local rate of transfusion after primary THA in 2013, referring to the number of patients undergoing THA at LHSC-UH needing a minimum transfusion of 1 unit of pRBC either intra- or postoperatively, is 4.2% (unpublished data). Powering a clinical trial with this as a primary outcome would require a very large sample size and heavy cost burden, not possible in this trial given the available funding opportunities. However, it remains an important outcome measured in this study because of its clinical applicability. Preoperative autologous blood donation is not considered part of the perioperative blood conservation protocol at LHSC-UH; a patient would be excluded from TeACH-R study participation if this treatment modality is part of the preoperative care plan.

3.6.3.2   Complications

Total hip arthroplasty is considered major orthopaedic surgery, carrying with it the risk of intra- and postoperative complications. However, when considering the addition of a new agent to a protocol, it is important to factor in the potential for adverse events as a result

of the intervention. Table 3.5 describes the complications recorded as part of the TeACH-R study protocol. These are included in our analysis were selected due to clinical impact; all listed events require a significant change in treatment protocol, possibly further surgical intervention. Of particular interest is the incidence of venous thromboembolic events (VTEs) in the postoperative period, although the investigators expect a very low incidence given the success of the current thromboprophylactic regimen. The incidence of intraoperative complications is drawn from the Operative Report, while postoperative in-hospital complications are noted from clinical progress notes and the Discharge Summary. As mentioned in 3.5.4, postoperative complications are tracked up to the 3-month mark postoperatively.

Table 3.5: TeACH-R Recorded Complications.

Intraoperative Complications
Fracture
Acute cardiorespiratory event
Neurologic injury
Vascular injury
Postoperative Complications
Venous thromboembolic event
Skin and soft tissue infection
Deep joint infection requiring revision hip surgery
Acute coronary syndrome
Acute respiratory depression
Acute renal failure
Pneumonia
Acute cerebrovascular accident (stroke) or transient ischemic attack
Wound hematoma
Seizure
Compartment syndrome

3.6.3.3   Inpatient Length of Stay

There are potential benefits associated with a shorter inpatient stay postoperatively, including a reduced risk of nosocomial infection[91, 92] and decreased cost, both important factors to consider in a publicly funded health care model with limited resources. Because TeACH-R participants are undergoing an elective procedure requiring admission to hospital, comparing length of stay against the standard of care is an important metric to

consider when testing a new intervention that may affect the postoperative course, which explains its inclusion in the TeACH-R final analysis.

3.7 Statistical Analysis

Appropriate statistical analysis enables the researcher to deduce reasonable conclusions based on the data collected throughout the course of a study. The TeACH-R trial is a prospective RCT with the goal of comparing two independent sample populations, meant to be representative of the population of individuals undergoing primary cementless THA, for a variety of nominal, ordinal and continuous variables. The samples are mutually exclusive; a patient can only be enrolled in one treatment arm throughout the course of the study. Data analysis follows a per protocol design, meaning that participant data is analyzed based on the treatment a participant receives, not to the treatment arm to which he or she is allocated to in the event of treatment arm crossover. This is in comparison to the intention-to-treat protocol commonly used in larger clinical trials, meant to provide a more conservative assessment of treatment effect. Because both treatment arms used in this study consist of administering a medication in a single-dose regimen by the treating surgeon, using the intention-to-treat protocol to decrease the effect of poor patient compliance is not needed in this study. Therefore, data from a study participant is analyzed based on the treatment he or she has received intraoperatively.

3.7.1 Sample Size Calculation

Determining sample size prior to commencement of a study, especially for a randomized clinical trial with data collected prospectively, is of critical importance. The concept of statistical power relates to the ability to decrease the chance of making a Type II error, and is dependent on three factors: sample size, effect size, and level of significance. Sample size is a major contributor to power in that increasing sample size has the effect of increasing the probability of detecting a difference in outcome (if one actually exists),

while maintaining a defined level of significance[93]. Type II errors, the acceptance of a false null hypothesis, are unfortunately commonplace in clinical research. Errors in study methodology, data analysis and the influence of confounding factors can affect the power of a study. The latter is defined as the ability to detect a difference in outcome if such a difference actually exists. Best efforts must be made in order to avoid making incorrect conclusions about a sample population that is either not representative of the target population, or is not large enough to detect a statistically or clinically significant difference.

For the TeACH-R trial, the sample size calculation used is shown in Figure 3.5. This is the sample size calculation for an unpaired, two-tailed *t test* for two independent sample populations, based on the primary outcome variable used in this study, ΔHgb. This statistical test will allow us to identify a difference in the mean ΔHgb in each of our treatment groups, as well as difference in calculated blood loss. The effect size drives the sample size calculation. In a previous study from LHSC-UH by Ralley et al, administration of intravenous TEA prior to the start of THA resulted in a significant reduction in ΔHgb[46]. Importantly, the dosing regiment of TEA used in this study is identical to that used in the TeACH-R trial. Cohen, in his 1988 book, provides a formula for calculating the *d* statistic, a measure of effect size assuming normal distribution in the sample, using the means and standard deviation of continuous variables. Computing the results from this study into the calculation for Cohen's results in an effect size of 0.58 (not shown), a moderate effect size[93]. Assessing effect sizes similar to this, the investigators determined that performing the sample size calculation with an effect size of 0.52, as presented in Figure 3.5, would allow for a sample size large enough to be able to detect a clinically meaningful difference between our two treatment groups, while staying within the allowable margins of unavoidable logistical and financial constraints.

In addition to effect size, other important considerations in interpreting this calculation include level of significance and power. The level of significance is set at $\alpha = 0.05$, the standard for reporting RCTs. There is a then a 5% that the resultant outcome is due to chance alone, equivalent to a *p* value less than 0.05 as the determinant of statistical significance. In a two-tailed analysis, the α level is split between the two ends of the

normal distribution. We suspect, in theory, that if the topical group were to be different for the primary outcome of blood loss, it would be more likely deemed inferior to the intravenous group. However, there is no evidence to support this judgment formed solely based on lack of experience in using the drug in this fashion. While a one-tailed analysis, more powerful in nature, would allow us to get away with a smaller sample size, it implies that we have a clear idea in which direction the test treatment will differ from the control group. A two-tailed analysis provides a more conservative measure of assessment, as the TeACH-R investigators do not know in which direction the topical group will differ from the intravenous group with regards to blood loss. Statistical power is set at $\beta = 0.80$, implying that there is an 80% chance of identifying a difference in outcomes between our two independent samples, should one actually exist. This is also the standard for reporting RCTs.

$$n = 2(Z_{(1-\alpha/2)} + Z_{(1-\beta)})^2 / (ES)^2$$
$$\text{where } Z_{(1-\alpha/2)} = 1.96 \ (\alpha = 0.05),$$
$$Z_{(1-\beta)} = 0.84 \ (\beta = 0.80), \text{ and}$$
$$ES = 0.52*$$

Solving for $n = 60$ per group.
Assuming 10% loss to follow-up,
$n = 144$ TeACH-R Participants

Figure 3.5: TeACH-R Sample Size Calculation. *Effect size of 0.52 determined based on results of ΔHgb from Ralley, F et al. *CORR* 2010; 468: 1905-1911.

This study is powered to detect a difference in the primary outcome variable, ΔHgb. To put it into perspective, an effect size with a standard score of 0.52 is analogous to a ΔHgb of just over 6 mg/dL. In terms of measured blood loss, this effect size corresponds to

approximately 300 mL of blood, using the randomized controlled trial by Johansson et al comparing intravenous TEA to placebo for total blood loss is as the point of reference[60]. To the TeACH-R investigators, this magnitude of difference for both variables not only represents a meaningful statistical difference, but also one that is clinically significant. Random sampling of 144 participants (or 72 per group) proceeding to THA would allows us to detect a clinically significant difference, should it exist, for either of our primary outcome measures. Importantly, the TeACH-R trial is not powered to detect a difference in any of the secondary outcome measures listed in Section 3.6.3.

The assumption of normal distribution is also important to take into consideration. As a general rule, a sample size of randomly selected subjects over 30 is deemed to show a normal distribution for a given variable. The stringent criteria for participant selection, in addition to the unbiased randomization protocol ensures that, even in this interim analysis, the sample drawn is representative of the population of interest, where the dependent primary outcome variables (ΔHgb, calculated blood loss) are assumed to adhere to the principle of normal distribution.

3.7.2 Outcome Comparison

3.7.2.1   Frequency Data

Not all variables assessed in the TeACH-R trial are measured on a continuous scale. Frequency data are not amenable to analysis via traditional comparison of means. The Pearson Chi-Square test is used to compare our two treatment arms when variables are measured at the nominal level. In essence, it allows the comparison of observed versus expected frequencies, using the same level of significance of ($p < 0.05$) as the sample size calculation above. The Chi-Square analysis, however, mandates an appropriate sample size for appropriate calculation of the test statistic. If an expected frequency was less than 5, Fisher's Exact Test was used to elucidate a potential difference between groups, again using the same level of significance. This latter test is well known to provide more appropriate results when smaller samples are compared[94].

3.7.2.2   Comparison of Means

The foundation of the TeACH-R data analysis is in the comparison of means. For this, we used a two-tailed, unpaired Student's t test to assess for any between group differences for all continuous variables. This includes both primary outcome measures. The Student's t test provides a mathematically identical result to a one-way analysis of variance (ANOVA). No variable was identified as having significant influence on the primary outcome variable; an analysis of covariance (ANCOVA) was therefore not appropriate for use in this study. The probability level used for comparison is 0.05, where a significant difference between groups is represented by $p < 0.05$.

3.7.2.3   Statistical Software

IBM SPSS Statistics, version 22 (IBM Canada Ltd., Markham, Ontario, Canada) was used to perform all statistical analysis for the TeACH-R study.

4 Results

4.1 Treatment Arm Allocation

Figure 4.1 displays the results of randomization. At time of interim analysis, 52 participants had completed the initial phase of the TeACH-R protocol, meaning that they had received the treatment, completed a period of convalescence in hospital, and were discharged. Thirty-two participants form the current cohort having received intravenous tranexamic acid, while 20 subjects received the topical regimen intraoperatively.

Drawing attention to key features within Figure 4.1, a relatively high proportion of screened patients were excluded from TeACH-R study participation (60/120, 50%). The predominant reason why screened patients were deemed ineligible for study participation was ineligibility to receive TEA in 21/60 (35%) of potential participants. The most common reason for not being eligible to receive TEA is a prior diagnosis of DVT or PE (7/60, 11.6%; data not shown). A diagnosis other than primary OA, RA or AVN excluded 12 of 60 (20%) of ineligible patients; most commonly, post-traumatic OA was the primary diagnosis (6/60, 10%; data not shown).

Eight of sixty (13.3%) of enrolled participants withdrew from formal study participation after being assigned a unique TeACH-R identifier. Data was not collected for these former participants. Most often, the reason for study exclusion was a problem in obtaining informed consent prior to the procedure; two enrolled participants withdrew from the study upon entry into the OR, and in one participant consent was lost postoperatively. On three occasions, a contraindication to either study participation or TEA administration altogether was identified only after the patient had consented to TeACH-R study participation.

Forty-seven of 52 (90.4%) of enrolled TeACH-R participants received the treatment assigned to them via the process of randomized treatment arm allocation. All five subjects who received the alternate treatment were slated to receive TEA topically, but instead were given TEA intravenously prior to the start of the procedure. Interestingly,

three of these participants were within the first block of 20 randomized participants, with the other two treatment arm crossovers occurring in the second round of block randomization, prior to the 40th randomized participant (data not shown). No instances of treatment arm crossover were recorded in the third block randomization sequence.
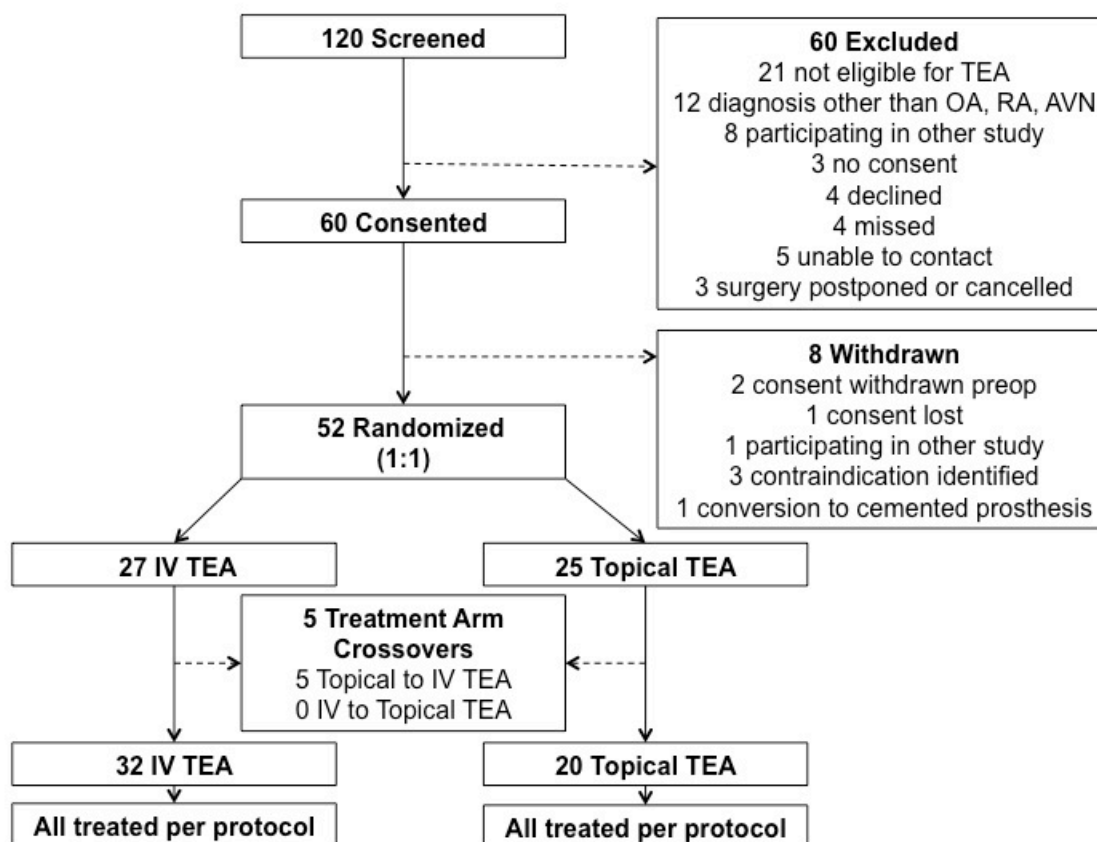

Figure 4.1: TeACH-R Treatment Allocation Flow Chart.

4.2 Demographics

Table 4.1 outlines the group comparisons for the listed demographic variables collected as part of the TeACH-R protocol. At baseline, the two treatment arms are similar for all variables.

Table 4.1: Demographic Characteristics for the TeACH-R Trial Sample Population.

	Intravenous Tranexamic Acid (*n* = 32)	Topical Tranexamic Acid (*n* = 20)	*p* value
Mean Age, years ± SD	63.8 ± 8.7	68.2 ± 9.3	0.087
Gender, *n* (%)			
Male	17 (53.1)	7 (35.0)	0.202
Female	15 (46.9)	13 (65.0)	
THA Laterality, *n* (%)			
Right	18 (56.3)	12 (60)	0.790
Left	14 (43.8)	8 (40)	
Mean Body Mass Index (kg/m^2, ± SD)	31.2 ± 7.1	29.2 ± 6.6	0.326
Mean Body Surface Area (m^2, ± SD)	2.08 ± 0.31	1.98 ± 0.26	0.246
Primary Diagnosis, *n* (%)			
OA	31 (96.9)	19 (95%)	
RA	0	0	0.732
AVN	1 (3.1)	1 (5%)	
Mean Charlson Age-Comorbidity Index	3.2 ± 1.4	3.7 ± 1.0	0.249
Mean ASA Score	2.4 ± 0.6	2.3 ± 0.5	0.368
Type of Anaesthesia, *n* (%)			
Regional (Spinal)	23 (71.9)	17 (85.0)	0.274
General	9 (28.1)	3 (15.0)	
Mean Procedure Time (h:mm, ± SD)	1:08 ± 0:13	1:10 ± 0:10	0.473
Acetabular Screw Placement, *n* (%)	7 (21.9)	4 (20.0)	0.872
Mean Preoperative Hgb, mg/dl ± SD	145.09 ± 12.6	142.45 ± 11.9	0.457
Preoperative Anemia	3 (9.4%)	0	0.224
Preoperative Hct, ± SD	0.432 ± 0.40	0.426 ± 0.36	0.565
DVT Prophylaxis, *n* (%)			
Factor Xa Inhibitor	31 (96.9)	20 (100)	0.425
Low Molecular-Weight Heparin	1 (3.1)	0	

Important to note in Table 4.1 is the lack of any statistical significant difference between our two groups with regards to the demographic variables. Almost all participants had a primary diagnosis of osteoarthritis and received rivaroxaban, a FXa inhibitor, as thromboembolic prophylaxis for the duration of the postoperative course. However, at the time of interim analysis, the topical group had a slightly higher proportion of females than males, the opposite of the intravenous group. This difference did not reach statistical significance. Although both groups demonstrated similar mean scores on the Charlson Age-Comorbidity Index, all three participants that were anemic preoperatively

were allocated to the intravenous TEA group. Although this difference did not meet statistical significance, it does suggest that the groups have a slight baseline difference in health status. Despite the presence of these 3 anemic participants in the intravenous group, the mean preoperative hemoglobin level is not shown to be different between groups.

4.3 Primary Outcome Measures

4.3.1 Delta-Hemoglobin

Delta-hemoglobin (ΔHgb) is defined as maximal drop in hemoglobin occurring during the immediate postoperative period. The lowest measured Hgb in hospital is subtracted from the Hgb value drawn nearest the operative date and time to obtain this measure for every TeACH-R subject. The mean of all ΔHgb values are compared between patients receiving intravenous and topical TEA as the primary outcome measure of the TeACH-R trial.

No significant difference in mean ΔHgb between the intravenous and topical groups was found (34.81±13.78 mg/dL vs. 35.65±15.54 mg/dL; $p = 0.840$). Given the wide error bars, a boxplot was used to identify any outliers that may be acting as confounders. The boxplot reveals similar features for both treatment groups, with 2 minor outlying values and 1 major outlying value contributing to the intravenous group.
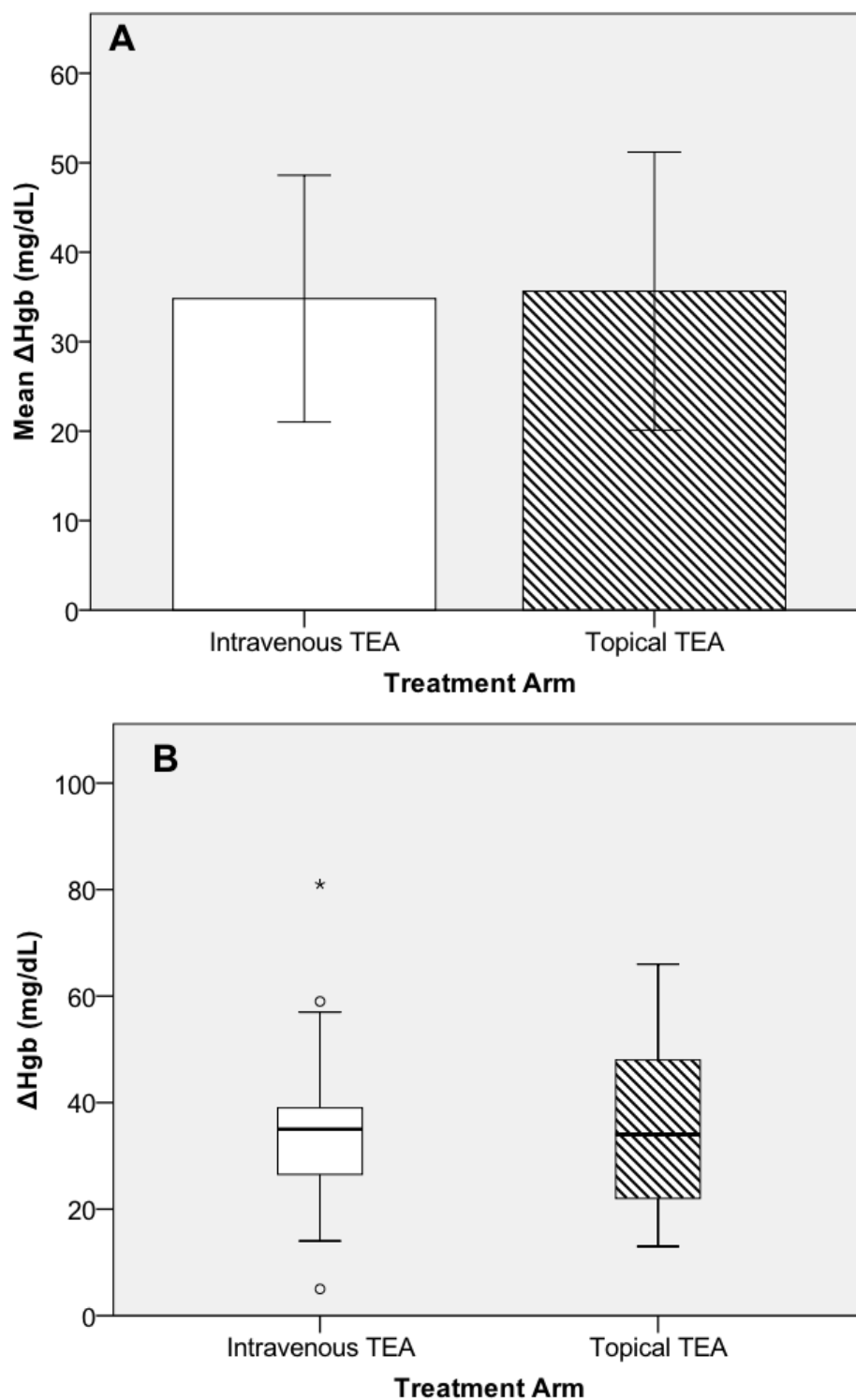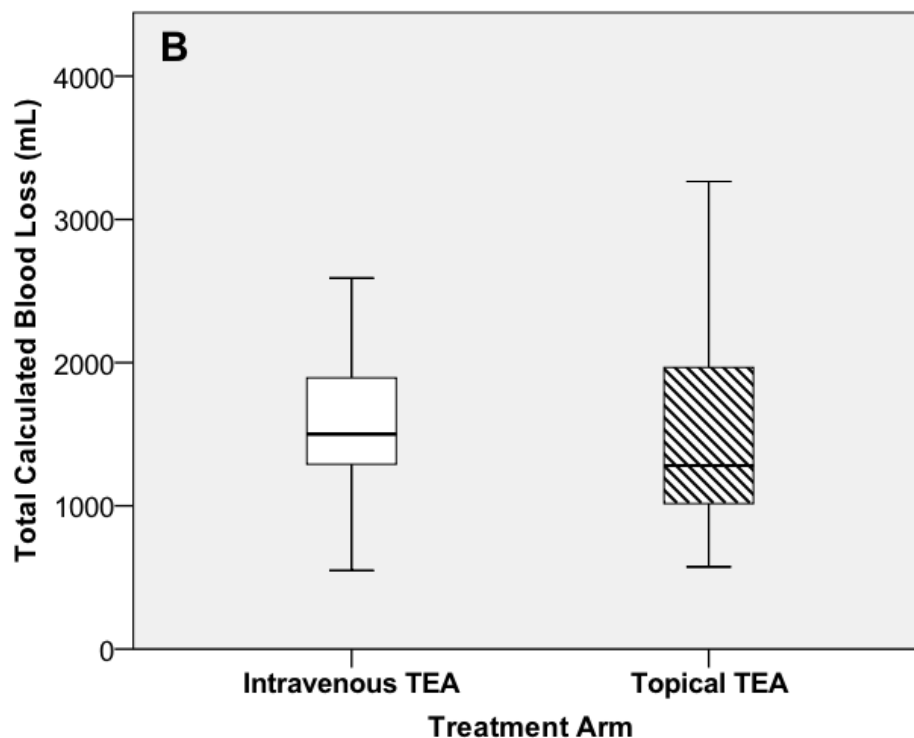
Figure 4.2: Postoperative Drop in Hemoglobin (ΔHgb) Following Intravenous and Topical Tranexamic Acid Administration in Total Hip Arthroplasty. No significant difference in the means of both treatment groups is identified (**A**), but boxplot analysis (**B**) reveals the presence of minor and major outliers within the treatment arm receiving intravenous TEA.

4.3.2 Calculated Blood Loss

Perioperative blood loss was calculated by the method described by Rosencher, as described in Section 3.6.2.2 and Figure 3.4. Mean blood loss, for all TeACH-R participants regardless of treatment arm allocation, was 1538 mL. No significance difference in mean calculated blood loss was identified between the intravenous and topical TEA treatment arms (1548±509 mL vs. 1521±693 mL; $p = 0.873$). Significant variability was noted, given the size of the error bars. Further boxplot analysis does not identify any significant outliers contributing to this variability.
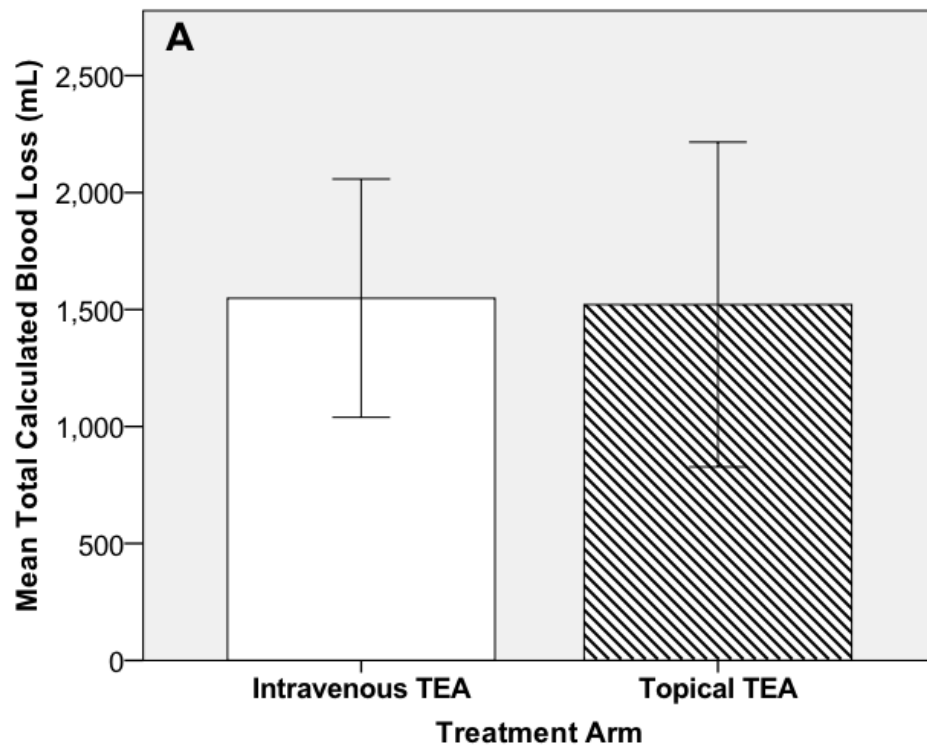
Figure 4.3: Calculated Blood Loss Following Intravenous and Topical Tranexamic Acid Administration in Total Hip Arthroplasty. No significant differences in the means of both treatment groups (**A**), although both show significant variability in the amount of blood lost in the perioperative period (**B**).

4.4 Secondary Outcome Variables

4.4.1 Length of Stay

Length of stay after THA averaged approximately 55 hours for both groups. There was no significant difference between those participants having received intravenous vs. topical TEA (55.0 ± 11.44 vs. 54.5 ± 20.1 hours; $p = 0.912$).
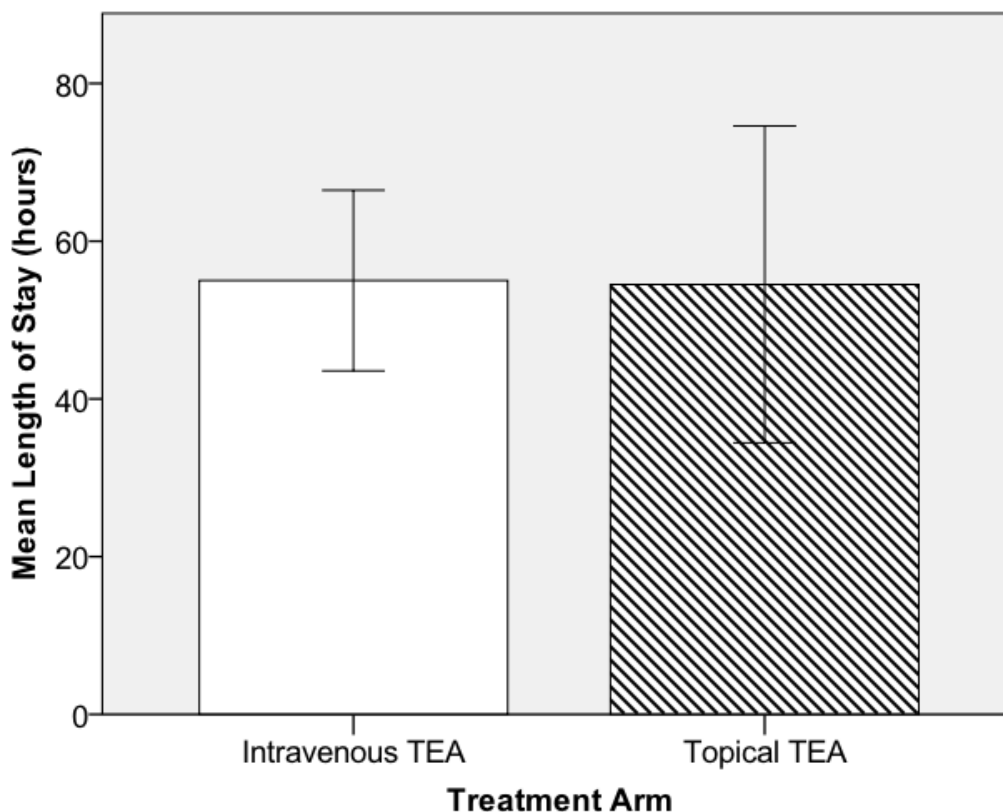
Figure 4.4: Length of Stay After Administration of Intravenous and Topical Tranexamic Acid During Total Hip Arthroplasty.

4.4.2 Transfusion Outcomes

At this time point in the TeACH-R trial, no patient in either group has required a transfusion of blood products during the postoperative in-hospital stay. Consequently, there have been no violations in the restrictive transfusion protocol.

4.4.3 Complications

At this point in the process of data analysis, 4 out of 52 (7.7%) TeACH-R study participants have suffered perioperative complications; 2 were deemed to occur intra-operatively, and 2 in the postoperative period. None of these complications consisted of VTE. There was no statistical difference in the incidence of perioperative adverse events between the intravenous and topical TEA treatment arms. One participant having

received topical TEA had a questionable intraoperative fracture identified on the routine postoperative radiograph of the pelvis. The weight bearing status of the participant was changed in the early postoperative period to protect against any component migration or crack propagation through the floor of the acetabulum. Given the change in management required as a result of this postoperative finding, this was recorded as a complication. Subsequently, another patient in the topical group developed a foot drop in the early postoperative period. A foot drop splint was applied and the patient was discharged with the diagnosis of sciatic neuropraxia. No further surgical intervention was required. A third patient in the topical group developed a significant thigh hematoma requiring close vigilance, but without the need for any additional treatment. The sole complication in the intravenous group consisted of a deep joint infection requiring urgent irrigation and debridement.

5 General Conclusions and Discussion

Interim analysis of data contained within a large-scale study is an important undertaking to ensure appropriate study progress. It allows the early identification of possible deficiencies in data collection, management and analysis, while at the same time giving some perspective on preliminary outcomes. In an RCT with a well-developed protocol, where the outcome data is objective and the research team responsible for data collection and analysis functions independent from the treating physician, minimal bias is introduced and valuable information can be gained by performing such an interval assessment of progress.

As the TeACH-R trial approaches the midway point in the recruitment period, promising results arise from the preliminary analysis. In primary elective total hip arthroplasty using cementless prosthetic components, the ability to decrease the postoperative hemoglobin drop (ΔHgb) and reduce surgical blood loss appears similar when topical TEA is administered by the treating surgeon directly into the joint at the end of the procedure, compared to the current standard of care of a weight-based dose of TEA administered intravenously by the attending anaesthesiologist prior to skin incision. In terms of the secondary outcome measures, no statistically or clinically significant difference in length of stay or thromboembolic complication rate was identified between the two treatment groups. Moreover, no transfusion of allogeneic pRBC was required in either group during the postoperative period. Despite these findings, a conclusion of therapeutic equivalence or non-inferiority would be erroneous in the setting of preliminary data analysis, as will be discussed in the following chapter.

5.1 Clinical Relevance

Blood conservation is an important consideration in the care of the arthroplasty patient. As evidenced in previous chapters, TEA plays an important role the perioperative blood conservation protocol at LHSC-UH. This study aims to determine whether or not TEA,

an antifibrinolytic agent, can be administered safely and effectively via the topical route at the end of THA. Analysis of the available data set shows that topical TEA is, by all accounts, effective and safe when compared to the current standard of care, intravenous TEA, in a standard population of patients having THA. Though there is anecdotal suggestion that administration of the TEA solution makes wound closure slightly more difficult for the deep muscle and capsule tissue layers during the time solution bathes the joint area, administering the drug in this manner has significant advantages.

First, topical administration allows direct action on bleeding vessels in tissues around the hip joint traumatized by aggressive incision, tissue retraction, and osteotomy. During the surgical approach, best attempts are made to incise through natural tissue planes to get down to the bone of the proximal femur. However, in trans-muscular approaches such at the modified direct lateral approach to the hip, incising through muscle is unavoidable, risking injury to smaller vessels. In the superficial muscular layers of the hip, cautery or ligation of bleeding vessels is done with relative ease; most of the time, surgical bleeding from these sources is identified and stopped prior to exposure of the hip joint. More problematic are the deeper tissues and bony structures of the hip, incised later in the operation. Surgical incision of capsular tissues around the hip during arthroplasty creates potential spaces able to accommodate a significant amount of blood loss in anatomic areas not always visible or accessible to the surgical team. This can result in a significant amount of unnoticed blood loss during and after hip replacement, in addition to the relative inability to stop continued blood loss from raw cancellous bone. By administering topical TEA into the hip joint and surrounding tissues at the end of the procedure, antifibrinolytic activity can be targeted onto these occult periarticular sources of bleeding during the postoperative period, without having to be administered intravenously. As has been shown by the current results of the TeACH-R trial, this strategy of applying a topical antifibrinolytic appears to be relatively effective, a promising avenue of treatment.

The second, and arguably more important advantage to topical administration of TEA relates to the theory that local administration of a drug results in concentrated activity at the site of application, with decreased levels of systemic absorption compared to the same

drug administered intravenously. Reliance on diffusion of TEA from the intravascular compartment to the joint space is less effective than applying the drug directly to the joint, the source of a significant amount of postoperative bleeding in arthroplasty-related procedures. It has been determined, in studies where TEA used to counter the fibrinolytic response after cardiopulmonary bypass, that TEA follows a two-compartment model of distribution[95, 38]. In simple terms, diffusion into and elimination from a compartment is dependent on transfer constants related to the permeability of the tissues and the physical characteristics of the substance. For the purpose of TEA use in total joint arthroplasty, this implies an unpredictable concentration of TEA within the operative joint when the drug is administered intravenously. Administration of the same drug topically means that the drug is not dependent on diffusion into the joint to be able to exert its action where it is needed the most, at a concentration that is predictable.

In addition to its effect on blood loss, there is concern that TEA has the ability to stabilize clots at sites distant to the surgical wound, increasing the risk of thromboembolic events when used in arthroplasty-related procedures. Thus far in the TeACH-R trial, no participant has been diagnosed with either a deep vein thrombus or pulmonary embolism, which is reassuring. Best efforts are made to balance clinical efficacy and systemic load for TEA, even though robust meta-analysis data has never proven an increased risk of thromboembolic complications resulting from TEA administration in THA. In addition to this postulated risk, there has also been suggestion of increased seizure activity when TEA is administered intravenously at a higher dose, further emphasizing the need for development of protocols that administer the correct dose for a particular patient, using the correct route of administration, for fear of causing side effects with administration of a toxic dose. Though there are few studies that have defined the absorption profile when TEA in given in THA, we can extrapolate a significant amount of information about the pharmacokinetic properties of TEA from the aforementioned studies in cardiac surgery, as well as from the study by Wong et al, who quantified plasma TEA levels after topical administration of the drug in TKA[39]. Thanks to these studies, we know there is some truth for TEA administered locally at the surgical site having significantly less systemic absorption than the intravenous form of the same drug, and that increasing the dose of a local TEA does not always parallel the expected clinical benefit. At the very least, our

results show that at a dose analogous to that used for intra-articular administration in TKA, clinical efficacy of topical TEA appears to be comparable to that afforded by intravenous TEA, without an increase in thromboembolic complications. We would expect the systemic load of TEA of our topical treatment arm to be similar to the 1.5-gram intravenous TEA arm of the Wong study, although we do not currently have the data to support this claim.

Despite these theoretical risks, intravenous TEA remains a valuable adjunct in our perioperative blood conservation protocol for patients having THA and TKA. At LHSC-UH, it is widely regarded as a safe drug when given to the right patient. Since its inception as standard of care for perioperative blood conservation in lower extremity joint arthroplasty at LHSC-UH, the influence of intravenous TEA in the arthroplasty patient population has resulted in improved surgical outcomes, including but not limited to lower ΔHgb and postoperative transfusion rates, with minimal downside. A large part of this success is due to the stringent preoperative medical review performed by not only the surgical team, but also by the clinicians working within the Perioperative Blood Conservation Program.

An important issue that remains to be determined is precisely who can receive intravenous TEA, topical TEA, or neither. Interim analysis of the TeACH-R trial has shown that a significant proportion (35%) of patients having elective primary THA have a documented contraindication to receiving intravenous TEA as per the TeACH-R protocol, and are not able to benefit from the drug. It is possible that some of these patients not eligible for intravenous TEA could benefit from topical TEA, if a decreased systemic load can be proven with the latter form of treatment. There just simply is not enough guidance available in the literature to support giving TEA to these patients deemed to have an elevated risk of adverse events, even though there may not be any absolute contraindication present within the medical history. Admittedly, given the novel application of topical TEA in THA for the TeACH-R trial, the exclusion criteria for this study are decidedly conservative, seeking to enroll participants who fit the medical profile of the standard arthroplasty patient, without any overt contraindications to TEA administration. Further investigation into the potential benefit of administering topical

TEA in a more liberal fashion could be warranted, but this is ultimately dependent on the final analysis of the TeACH-R trial, which will only be available once the predicted sample size of 144 participants is achieved.

For the majority of THA patients that can take the drug, weight-based intravenous administration will likely remain a mainstay of therapy, even with the promising outcomes that have come in this interim analysis. The single-dose TEA protocol has been well received by both surgeons and anaesthesiologists alike, not only because of the significant clinical benefit, but also due to the relative ease of use. The process of formal adoption of a novel form of therapy is dependent not only on the results of high-quality RCTs, but also on surgeon preference. However, it will be interesting to re-assess the results once all data has been collected, in order to determine whether or not these preliminary outcomes hold true once statistical power is reached for our sample population. If they do, there may be a role of topical TEA as an alternate to intravenous TEA for select patients undergoing THA.

5.2 TeACH-R Trial Analysis and Design

Commonly, an RCT seeks to determine superiority over the accepted standard of care beyond a reasonable doubt. This reasonable doubt, in statistical terms, is the level of significance. When there is no standard of care, determination of superiority over no treatment, or placebo, provides the impetus for a change in the standard of care. Importantly, acceptance of the null hypothesis for a superiority trial is not to be confused with therapeutic equivalence; after all, as the statistical axiom stipulates, absence of evidence does not equal evidence of absence.[94]

In certain circumstances, a form of treatment exists that is widely accepted as the standard of care for the population under study. If a study participant is eligible to receive the standard of care, but is assigned to the placebo arm of the study, serious ethical implications arise due to withholding treatment with known benefit. At LHSC-UH, a patient undergoing THA that is able to safely receive TEA intravenously based on

their preoperative risk profile will receive the drug as standard of care. However, topical administration of TEA has postulated benefits: decreased systemic absorption and local action on bleeding vessels are generally desired characteristics of a drug administered to stop surgical bleeding. The goal of the TeACH-R RCT is to determine whether our test group, participants receiving topical TEA, show a difference with regards to blood loss compared to the active agent acting as the standard of care, intravenous TEA.

Initially, the investigators favored a non-inferiority trial design, where the goal is not to prove superiority, but instead to determine whether topical TEA is inferior to intravenous TEA with regards to blood loss in THA. However, clinical trials of this variety depend on the rate of an event occurring, in order to determine the odds ratio of said event occurring when the novel treatment is given compared to the standard of care. In the end, we wish to determine the net benefit of the new treatment, defined as the absolute risk difference. ΔHgb, a continuous measure, is not amenable to determination of risk reduction. Clinically important event rates for the TeACH-R trial would include the incidence of postoperative transfusion, or the incidence of thromboembolic phenomena as a consequence of treatment in either arm. With the advances in patient care that have come about in the field of orthopaedic surgery, as well as a renewed focus on the medical care of the orthopaedic patient, these adverse events are a relative rarity. The sample size required to prove a marginal clinical benefit for these variables is unfortunately beyond the limits of the available resources for the TeACH-R study.

The ΔHgb and calculated blood loss, on the other hand, provide sensitive parameters to test our hypothesis, with the requirement of far fewer patients in each of our treatment arms. Between-group differences in these primary outcome measures also have the potential to change management, should the results reach clinical significance. In this interim analysis, we get the initial impression that topical TEA has the potential to be an efficacious alternative to intravenous TEA for reduction of blood loss in patients having primary THA, for both aforementioned variables, with little risk of adverse events. However, caution must be taken in interpreting these interim results, as statistical power has yet to be achieved for our sample population.

5.3 Strengths of the TeACH-R Study

Results emanating from the TeACH-R trial will contribute significantly to understanding the role and importance of perioperative blood conservation in the arthroplasty patient. With the gradual increase in use of TEA as a valuable adjunct to perioperative blood conservation programs, high quality RCTs will become paramount in supporting or refuting novel therapeutic regimens for TEA. Unfortunately, there are a great number of clinical trials on the topic, although few are of high-enough quality to effectively change management. Although a significant number of trials have shown promise when TEA is given in THA, the variety of treatment protocols makes it difficult to deduce which route of administration is more effective as an adjunct in controlling perioperative blood loss. This study will clarify how TEA can be administered most effectively for the patient having elective primary THA.

The TeACH-R trial is the first and only RCT designed as a direct comparison between topical and intravenous TEA in THA. There is supportive evidence for using both topical and intravenous TEA from studies assessing each form of treatment independent of the other, in placebo-controlled trials, but never have these two treatment alternatives been compared directly for these primary and secondary outcomes. In the quest to find the right form of TEA with optimal dosing, comparing all available modalities not only to placebo, but also to one another is an important step in determining which treatment is the standard of care for a given population.

Our sample size of 144 participants is powered to detect a clinically significant difference for two important primary outcomes: the drop in Hgb after hip replacement, and total blood loss. The assessment of blood loss has traditionally been measured by imperfect means, and unfortunately these results have permeated the literature surrounding this topic, often resulting in a significant underestimation of the magnitude of blood loss. The TeACH-R trial protocol uses a robust formula for calculating blood loss using proven research methodology to get the most reliable estimate, further increasing the validity of the treatment comparison. Furthermore, the large sample size helps in decreasing

variability in our results, and ensures a normal distribution for the continuous variables studied.

The well-developed prospective study design of this trial also strengthens the validity of the results by minimizing bias due to errors in study methodology. The stringent TeACH-R protocol ensures that randomization and blinding are maintained throughout the duration of the study. In combination with the objective nature of the data collected, there are few sources of bias even with a single-blinded protocol. The stringent inclusion and exclusion criteria for the TeACH-R trial isolate the population representative of the majority of patients proceeding to THA for whom perioperative administration of TEA is indicated.

5.4 Limitations of the TeACH-R Study

The predominant limitation at this point in time is the size of the available data set. We have reached a sample size that allows comparison of the means for certain variables between the treatment arms on the basis of a normal distribution, but have not yet reached the size necessary to affirm our conclusions. In the end, our current sample is similar to the target population under study, but the ability to detect a statistically significant difference in each of our primary outcome variables is limited by the number of participants in each of our sample group. However, recruitment is proceeding well, and given that LHSC-UH is a high-volume Canadian center for total joint arthroplasty, it will not be long before data is available for the final analysis.

The TeACH-R study is not powered to identify any significant difference in any of our secondary outcome measures, given the infrequent nature of occurrence for these variables. Even though these outcomes are important, the sample size that would be required for detect a clinically significant difference for these variable is not possible given resource limitations.

Another important consideration is that the TeACH-R study does not have a placebo control group. As mentioned previously, when a treatment exists that is considered

standard of care, like is the case with intravenous TEA in THA at LHSC-UH, is becomes unethical to enroll a study subject in a placebo-controlled RCT when he or she would otherwise be eligible to receive the standard of care. Thankfully, data from the TRANX-H trial, published in 2013 with similar study methodology and outcome variables to the TeACH-R trial, showed that administration of topical TEA was indeed superior to placebo for blood loss and transfusion rate reduction in THA,[56] in addition to the number of studies that have shown benefit of intravenous TEA in THA for the same outcome variables. Early in the study development phase, there was consideration for an additional treatment arm where TEA would be applied earlier in the procedure at time of arthrotomy, instead of at the end of the procedure when the arthrotomy was closed. Amongst the arthroplasty surgeons at LHSC-UH that would be participating in this trial, it was felt that administering TEA at this time, with the mandatory 5-minute pause, would create an undue surgical delay with minimal perceived benefit. While not considered a limitation per se, the addition of this treatment arm would have provided relevant data with regards to timing of topical TEA administration. In all, the comparison between the two treatment arms in the TeACH-R study represents reliable and valid study methodology, even without a placebo group.

5.5 Final Remarks and Further Developments

Early in the study development phase, The TeACH-R investigators asked a research question: is topical TEA, administered directly into the hip joint, as effective at reducing blood loss compared to intravenous TEA? This simple question led to the development of a significant research endeavor that has shown significant progress in the twelve months since its inception.

The purported benefits of topical TEA are not only related to improved control of blood loss over intravenous TEA, but also on decreasing the potential complications that arise from administration of intravenous TEA. At the very least, we strive to ensure that this novel form of treatment is not inferior to the standard of care with regards to blood loss. At the time of interim analysis, the delivery of TEA topically at the time of arthrotomy

closure shows similar clinical benefits with regards to perioperative blood loss when compared to intravenous TEA in THA. Very few adverse events have been identified, with no difference between the two treatment arms of the TeACH-R trial for all the variables examined. Should the final analysis show similar findings once the sample size is large enough for the study to be adequately powered for the primary outcomes of ΔHgb and calculated blood loss, topical TEA could potentially play a significant role as a valuable adjunct for perioperative blood management in patients going for THA, in addition to the current standard of care, intravenous TEA.

Future developments are focused on defining the safety profile of TEA, beginning with the analysis of plasma TEA levels in patients receiving either topical or intravenous TEA during THA. This will allow further delineation of safe treatment regimens, and provide insight into the pharmacokinetic properties of TEA when used at the typical doses for perioperative blood conservation in THA.

In all, evidence from the interim analysis of the TeACH-R trial, supported by data from other studies, suggests that TEA administered both intravenously and topically can provide significant benefit to patients undergoing THA, all the while maintaining a favorable risk profile. Although much work has yet to be done in uncovering the intricacies in administering this antifibrinolytic agent safely, exciting opportunities certainly exist for further development in the field of perioperative blood conservation for arthroplasty patients. Exploring the clinical efficacy of alternative therapies like these could usher in a new way of helping the thousands of individuals who proceed to THA each day in Canada and across the world.

6 References

1.   Felson DT, Lawrence RC, Dieppe PA, et al.: Osteoarthritis: New Insights, Part 1: The Disease and Its Risk Factors. *Annals of Internal Medicine* 2000;133:635-646.

2.   Tarride JE, Haq M, O'Reilly DJ, et al.: The excess burden of osteoarthritis in the province of Ontario, Canada. *Arthritis and rheumatism* 2012;64:1153-1161.

3.   Buckwalter JA, Saltzman C, Brown T: The Impact of Osteoarthritis. *Clinical Orthopaedics and Related Research* 2004;427:S6-S15.

4.   Dorland I, Newman WA: *Dorland's Illustrated Medical Dictionary*. ed 31st Edition. Philadelphia: Saunders Elsevier, 2007.

5.   Canadian Institute for Health Information: *Hip and Knee Replacements in Canada: Canadian Joint Replacement Registry 2014 Annual Report*, 2014.

6.   Khanuja HS, Vakil JJ, Goddard MS, Mont MA: Cementless femoral fixation in total hip arthroplasty. *Journal of Bone and Joint Surgery* 2011;93:500-509.

7.   Pivec R, Johnson AJ, Mears SC, Mont MA: Hip arthroplasty. *The Lancet* 2012;380:1768-1777.

8.   Learmonth ID, Young C, Rorabeck C: The operation of the century: total hip replacement. *The Lancet* 2007;370:1508-1519.

9.   Charnley J: Arthroplasty of the Hip: A New Operation. *The Lancet* 1961;277:1129-1132.

10.   Hardinge K: The direct lateral approach to the hip. *Journal of Bone and Joint Surgery (British)* 1982;64-B:17-19.

11.   Nachbur B, Meyer RP, Verkkala K, Zurcher R: The Mechanisms of Severe Arterial Injury in Surgery of the Hip Joint. *Clinical Orthopaedics and Related Research* 1979;141.

12.   Weiskopf RB, Viele MK, Feiner J, et al.: Human Cardiovascular and Metabolic Response to Acute, Severe, Isolvolemic Anemia. *JAMA* 1998;279:217-221.

13.   McGilvray ID, Rotstein OD: Surgical Treatment: Evidence-Based and Problem-Oriented, in Holzheimer RG, Mannick JA (eds). Munich: Zuckschwerdt, 2001.

14.   Risberg B: The response of the fibrinolytic system in trauma. *Acta Chirurgica Scandinavica* 1985;522:245-271.

15. Benoni G, Lethagen S, Fredin H: The effect of tranexamic acid on local and plasma fibrinolysis during total knee arthroplasty. *Thrombosis Research* 1997;85:195-206.

16. Ellis MH, Fredman B, Zohar E, Ifrach N, Jedeikin R: The effect of tourniquet application, tranexamic acid, and desmopressin on the procoagulant and fibrinolytic systems during total knee replacement. *Journal of Clinical Anesthesia* 2001;13:509-513.

17. Falck-Ytter Y, Francis CW, Johanson NA, et al.: Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e278S-325S.

18. Mont MA, Jacobs JJ: AAOS Clinical Practice Guideline: Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty. *Journal of the American Academy of Orthopaedic Surgeons* 2011;19:777-778.

19. Eriksson BI, Borris LS, Friedman RJ, et al.: Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty. *New England Journal of Medicine* 2008;358:2765-2775.

20. Eriksson BI, Kakkar AK, Turpie AGG, et al.: Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. *Journal of Bone and Joint Surgery (British)* 2009;91B.

21. Spahn DR: Anemia and Patient Blood Management in Hip and Knee Surgery: A Systematic Review of the Literature. *Anesthesiology* 2010;113.

22. Carson JL, Duff A, Poses RM, et al.: Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *The Lancet* 1996;348:1055-1060.

23. Friedman R, Homering M, Holberg G, Berkowitz SD: Allogeneic Blood Transfusions and Postoperative Infections After Total Hip or Knee Arthroplasty. *The Journal of Bone and Joint Surgery* 2014;96:272.

24. Newman ET, Watters TS, Lewis JS, et al.: Impact of Perioperative Allogeneic and Autologous Blood Transfusion on Acute Wound Infection Following Total Knee and Total Hip Arthroplasty. *The Journal of Bone and Joint Surgery* 2014;96:279-284.

25. Vignali A, Braga M, Gianotti L, et al.: A single unit of transfused allogeneic blood increases postoperative infections. *Vox Sanguinis* 1996;71:170-175.

26. Innerhofer P, Walleczek C, Luz G, et al.: Transfusion of buffy coat-depleted blood components and risk of postoperative infection in orthopedic patients. *Transfusion* 1999;39:625-632.

27.   Carson JL, Terrin ML, Noveck H, et al.: Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery. *New England Journal of Medicine* 2011;365:2453-2462.

28.   Hebert PC, Wells G, Blajchman MA, et al.: A Multicenter, Randomized, Controlled Trial of Transfusion Requirements in Critical Care. *New England Journal of Medicine* 1999;340:409-417.

29.   Keating EM, Meding JB: Perioperative Blood Management Practices in Elective Orthopaedic Surgery. *Journal of the American Academy of Orthopaedic Surgeons* 2002;10:393-400.

30.   Oremus K, Sostaric S, Trkulja V, Haspl M: Influence of tranexamic acid on postoperative autologous blood retransfusion in primary total hip and knee arthroplasty: a randomized controlled trial. *Transfusion* 2014;54:31-41.

31.   Henry David A, Carless Paul A, Moxey Annette J, O'Connell D, Ker K, Fergusson Dean A: Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion, in *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd, 2001.

32.   Abul-Azm A, Abdullah KM: Effect of topical tranexamic acid in open heart surgery. *European journal of anaesthesiology* 2006;23:380-384.

33.   De Bonis M, Cavaliere F, Alessandrini F, et al.: Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study. *Journal of Thoracic & Cardiovascular Surgery* 2000;119:575-580.

34.   Dell'Amore A, Caroli G, Nizar A, et al.: Can topical application of tranexamic acid reduce blood loss in thoracic surgery? A prospective randomised double blind investigation. *Heart, Lung & Circulation* 2012;21:706-710.

35.   McCormack PL: Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. *Drugs* 2012;72:585-617.

36.   Dunn CJ, Goa KL: Tranexamic acid: a review of its use in surgery and other indications. *Drugs* 1999;57:1005-1032.

37.   Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M: High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesthesia and analgesia* 2010;110:350-353.

38.   Sharma V, Fan J, Jerath A, et al.: Pharmacokinetics of tranexamic acid in patients undergoing cardiac surgery with use of cardiopulmonary bypass. *Anaesthesia* 2012;67:1242-1250.

39.   Wong J, Abrishami A, El Beheiry H, et al.: Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. *The Journal of Bone and Joint Surgery* 2010;92:2503-2513.

40.   Mannucci PM: Hemostatic Drugs. *New England Journal of Medicine* 1998;339:245-253.

41.   Mangano DT, Tudor IC, Dietzel C: The Risk Associated with Aprotinin in Cardiac Surgery. *New England Journal of Medicine* 2006;354:353-365.

42.   Roberts I, Shakur H, Coats T, et al.: The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health technology assessment* 2013;17:1-79.

43.   Taghaddomi RJ, Mirzaee A, Attar AS, Shirdel A: Tranexamic acid reduces blood loss in off-pump coronary artery bypass surgery. *Journal of Cardiothoracic & Vascular Anesthesia* 2009;23:312-315.

44.   Fawzy H, Elmistekawy E, Bonneau D, Latter D, Errett L: Can local application of Tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial. *Journal Of Cardiothoracic Surgery* 2009;4:25.

45.   Fergusson DA, Hébert PC, Mazer CD, et al.: A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery. *New England Journal of Medicine* 2008;358:2319-2331.

46.   Ralley FE, Berta D, Binns V, Howard J, Naudie DD: One intraoperative dose of tranexamic Acid for patients having primary hip or knee arthroplasty. *Clinical Orthopaedics and Related Research* 2010;468:1905-1911.

47.   Ker K, Beecher D, Roberts I: Topical application of tranexamic acid for the reduction of bleeding. *Cochrane Database of Systematic Reviews* 2013;7:010562.

48.   Good L, Peterson E, Lisander B: Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. *British Journal of Anaesthesia* 2003;90:596-599.

49.   Aguilera X, Martinez-Zapata MJ, Bosch A, et al.: Efficacy and safety of fibrin glue and tranexamic acid to prevent postoperative blood loss in total knee arthroplasty: a randomized controlled clinical trial. *The Journal of Bone and Joint Surgery* 2013;95:2001-2007.

50.   Maniar RN, Kumar G, Singhi T, Nayak RM, Maniar PR: Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. *Clinical Orthopaedics and Related Research* 2012;470:2605-2612.

51.   Alvarez JC, Santiveri FX, Ramos I, Vela E, Puig L, Escolano F: Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. *Transfusion* 2008;48:519-525.

52.   Seo JG, Moon YW, Park SH, Kim SM, Ko KR: The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. *Knee Surgery, Sports Traumatology, Arthroscopy* 2013;21:1869-1874.

53.   Charoencholvanich K, Siriwattanasakul P: Tranexamic acid reduces blood loss and blood transfusion after TKA: a prospective randomized controlled trial. *Clinical Orthopaedics and Related Research* 2011;469:2874-2880.

54.   Georgiadis AG, Muh SJ, Silverton CD, Weir RM, Laker MW: A prospective double-blind placebo controlled trial of topical tranexamic acid in total knee arthroplasty. *Journal of Arthroplasty* 2013;28:78-82.

55.   Konig G, Hamlin BR, Waters JH: Topical tranexamic Acid reduces blood loss and transfusion rates in total hip and total knee arthroplasty. *Journal of Arthroplasty* 2013;28:1473-1476.

56.   Alshryda S, Mason J, Sarda P, et al.: Topical (Intra-Articular) Tranexamic Acid Reduces Blood Loss and Transfusion Rates Following Total Hip Replacement: A Randomized Controlled Trial (TRANX-H). *The Journal of Bone and Joint Surgery* 2013;95:1969-1974.

57.   Benoni G, Lethagen S, Nilsson P, Fredin H: Tranexamic acid, given at the end of the operation, does not reduce postoperative blood loss in hip arthroplasty. *Acta Orthopaedica Scandinavica* 2000;71:250-254.

58.   Ekback G, Axelsson K, Ryttberg L, et al.: Tranexamic acid reduces blood loss in total hip replacement surgery. *Anesthesia and analgesia* 2000;91:1124-1130.

59.   Imai N, Dohmae Y, Suda K, Miyasaka D, Ito T, Endo N: Tranexamic acid for reduction of blood loss during total hip arthroplasty. *Journal of Arthroplasty* 2012;27:1838-1843.

60.   Johansson T, Pettersson LG, Lisander B: Tranexamic acid in total hip arthroplasty saves blood and money: a randomized, double-blind study in 100 patients. *Acta Orthopaedica Scandinavica* 2005;76:314-319.

61.   Husted H, Blond L, Sonne-Holm S, Holm G, Jacobsen TW, Gebuhr P: Tranexamic acid reduces blood loss and blood transfusions in primary total hip arthroplasty: a prospective randomized double-blind study in 40 patients. *Acta Orthopaedica Scandinavica* 2003;74:665-669.

62.   Garneti N, Field J: Bone bleeding during total hip arthroplasty after administration of tranexamic acid. *Journal of Arthroplasty* 2004;19:488-492.

63.   Niskanen RO, Korkala OL: Tranexamic acid reduces blood loss in cemented hip arthroplasty: a randomized, double-blind study of 39 patients with osteoarthritis. *Acta Orthopaedica Scandinavica* 2005;76:829-832.

64.   Yamasaki S, Masuhara K, Fuji T: Tranexamic acid reduces postoperative blood loss in cementless total hip arthroplasty. *Journal of Bone & Joint Surgery* 2005;87:766-770.

65.   McConnell JS, Shewale S, Munro NA, Shah K, Deakin AH, Kinninmonth AW: Reduction of blood loss in primary hip arthroplasty with tranexamic acid or fibrin spray. *Acta Orthopaedica Scandinavica* 2011;82:660-663.

66.   Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W: Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. *Thrombosis Research* 2009;123:687-696.

67.   Ho KM, Ismail H: Use of intravenous tranexamic acid to reduce allogeneic blood transfusion in total hip and knee arthroplasty: a meta-analysis. *Anaesthesia and Intensive Care* 2003;31:529-537.

68.   Cid J, Lozano M: Tranexamic acid reduces allogeneic red cell transfusions in patients undergoing total knee arthroplasty: results of a meta-analysis of randomized controlled trials. *Transfusion* 2005;45:1302-1307.

69.   Gill JB, Rosenstein A: The use of antifibrinolytic agents in total hip arthroplasty: a meta-analysis. *Journal of Arthroplasty* 2006;21:869-873.

70.   Zufferey P, Merquiol F, Laporte S, et al.: Do Antifibrinolytics Reduce Allogeneic Blood Transfusion in Orthopedic Surgery? *Anesthesiology* 2006;105.

71.   Sukeik M, Alshryda S, Haddad FS, Mason JM: Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. *Journal of Bone & Joint Surgery (British)* 2011;93:39-46.

72.   Gandhi R, Evans HM, Mahomed SR, Mahomed NN: Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. *BMC Research Notes* 2013;6:184.

73.   Zhou XD, Tao LJ, Li J, Wu LD: Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. *Archives of Orthopaedic & Trauma Surgery* 2013;133:1017-1027.

74.   OCBEM Levels of Evidence Working Group: *The Oxford 2011 Levels of Evidence*, 2011.

75.   Namba RS, Paxton L, Fithian DC, Stone ML: Obesity and perioperative morbidity in total hip and total knee arthroplasty patients. *Journal of Arthroplasty* 2005;20:46-50.

76.   Wilson A, Yu HT, Goodnough LT, Nissenson AR: Prevalence and outcomes of anemia in rheumatoid arthritis: a systematic review of the literature. *The American journal of medicine* 2004;116:50S-57S.

77.   Harris ED: Rheumatoid Arthritis: Pathophysiology and Implications for Therapy. *New England Journal of Medicine* 1990;322:1277-1289.

78.   Bagot CN, Arya R: Virchow and his triad: a question of attribution. *British journal of haematology* 2008;143:180-190.

79.   Dahl OE, Aspelin T, Arnesen H, et al.: Increased activation of coagulation and formation of deep vein thrombosis following discontinuation of thromboprophylaxis after hip replacement surgery. *Thrombosis Research* 1995;80:299-306.

80.   Dahl OE, PEdersen T, Kierulf P, et al.: Sequential intrapulmonary and systemic activation of coagulation and fibrinolysis during and after total hip replacement surgery. *Thrombosis Research* 1993;70:451-458.

81.   Degroot V, Beckerman H, Lankhorst G, Bouter L: How to measure comorbidity: a critical review of available methods. *Journal of Clinical Epidemiology* 2003;56:221-229.

82.   Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases* 1987;40:373-383.

83.   Charlson M, Szatrowski TP, Peterson J, Gold J: Validation of a combined comorbidity index. *Journal of Clinical Epidemiology* 1994;47:1245-1251.

84.   Owens WD, Felts JA, Spitznagel EL: ASA Physical Status Classifications: A Study of Consistency of Ratings. *Anaesthesiology* 1978;49:239-243.

85.   Hu S, Zhang ZY, Hua YQ, Li J, Cai ZD: A comparison of regional and general anaesthesia for total replacement of the hip or knee: a meta-analysis. *Journal of Bone and Joint Surgery (British)* 2009;91-B:935-942.

86.   Guay J: The effect of neuraxial blocks on surgical blood loss and blood transfusion requirements: a meta-analysis. *Journal of Clinical Anesthesia* 2006;18:124-128.

87.   Gross JB: Estimating allowable blood loss: corrected for dilution. *Anesthesiology* 1983;58:277-280.

88.   Nadler SB, Hidalgo JH, Bloch T: Prediction of blood volume in normal human adults. *Surgery* 1962;51:224-232.

89.   Brecher ME, Monk TG, Goodnough LT: A standardized method for calculating blood loss. *Transfusion* 1997;37:1070-1074.

90.   Rosencher N, Kerkkamp HE, Macheras G, et al.: Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. *Transfusion* 2003;43:459-469.

91.   Jencks SF, Williams DK, Kay TL: Assessing hospital-associated deaths from discharge data: The role of length of stay and comorbidities. *JAMA* 1988;260:2240-2246.

92.   Safdar N, Maki DG: The Commonality of Risk Factors for Nosocomial Colonization and Infection with Antimicrobial-Resistant Staphylococcus aureus, Enterococcus, Gram-Negative Bacilli, Clostridium difficile, and Candida. *Annals of Internal Medicine* 2002;136:834-844.

93.   Cohen J: *Statistical Power Analysis for the Behavioral Sciences*. ed 2nd. New Jersey: Lawrence Erlbaum Associates, 1988.

94.   Munro BH: *Statistical Methods for Health Care Research*. ed 4th. New York: Lippincott Williams & Wilkins, 2001.

95.   Dowd NP, Karski JM, Cheng DC, et al.: Pharmacokinetics of Tranexamic Acid during Cardiopulmonary Bypass. *Anesthesiology* 2002;97:390-399.

Appendix A: List of Abbreviations

Apr	Aprotinin
ANOVA	Analysis of variance
ASA	American Society of Anaesthesiologists
BUN	Blood Urea Nitrogen
CBC	Complete blood count
Cr	Creatinine
DDH	Developmental dysplasia of the hip
DTI	Direct thrombin inhibitor
DVT	Deep vein thrombosis
EACA	Epsilon-aminocaproic acid
ESA	Erythropoietin-stimulating agent
FVII(a)	Factor VII (activated)
FX(a)	Factor X (activated)
FXaI	Factor Xa inhibitor
FXIII(a)	Factor XIII (activated)
Hct	Hematocrit
Hgb	Hemoglobin
IA	Intra-articular
INR	International Normalized Ratio

IT   Ilio-tibial

IV   Intravenous

LCPD   Legg-Calvé-Perthes disease

LHSC-UH   London Health Sciences Centre, University Hospital

LMWH   Low-molecular-weight heparin

OA   Osteoarthritis

ONP   Orthopaedic Nurse Practitioner

OR   Operating Room

PAC   Pre-Admission Clinic

PBCP   Perioperative Blood Conservation Program

PE   Pulmonary embolus

pRBC   Packed red blood cells

PTT   Partial thromboplastin time

RA   Rheumatoid arthritis

RCT   Randomized controlled trial

SCFE   Slipped capital femoral epiphysis

TEA   Tranexamic acid

TeACH-R   Tranexamic Acid Comparison in Hip Replacement (Trial)

TF   Tissue Factor

THA   Total hip arthroplasty

TKA   Total knee arthroplasty

UFH   Unfractionated heparin

VTE   Venous thromboembolic event

Appendix B: Ethics Board Approval

Western Research
Use of Human Participants - Initial Ethics Approval Notice

Principal Investigator: Dr. Douglas Naudie
File Number:104559
Review Level: Full Board
Protocol Title: Comparative Efficacy of Topical versus Intravenous Administration of Tranexamic Acid in Primary Total Hip Arthroplasty
Department & Institution: Schulich School of Medicine and Dentistry\Surgery,London Health Sciences Centre
Sponsor:
Ethics Approval Date: February 18, 2014
Ethics Expiry Date: October 31, 2015

Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Other	Chart Abstraction Form - 3 months	2013/10/16
Other	Chart Abstraction Form - 6 week follow-up	2013/10/16
Other	Chart Abstraction Form - Demographic Data	2013/10/16
Other	Chart Abstraction Form - In Hospital	2013/10/16
Other	Patient Questionnaire	2013/11/28
Letter of Information & Consent	Revised Letter of Information and Consent (CLEAN PDF COPY)	2014/02/05
Protocol	REVISED Full HSREB Form (CLEAN PDF COPY)version 3	2014/02/05

This is to notify you that the University of Western Ontario Health Sciences Research Ethics Board (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this HSREB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request form.

Member of the HSREB that are named as investigators in research studies, or declare a conflict of interest, do not participate in discussions related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Appendix C: TeACH-R Consent Form

Comparative Efficacy of Topical versus Intravenous Administration of Tranexamic Acid in Primary Total Hip Arthroplasty

Study Doctors
Dr. Douglas Naudie – London Health Science Centre
Dr. James Howard – London Health Science Center
Dr. Fiona Ralley – London Health Sciences Centre
Dr. Lyndsay Somerville – Sandy Kirkley Centre for Musculoskeletal Research
Dr. Richard Nadeau – Orthopaedic Surgery Resident
Study Coordinators
Katherine Hrabok
Abigail Korczak

Dear Patient:

You are being invited to voluntarily participate in a research study designed for patients undergoing a total hip replacement. This letter of information describes the research study and your role as a participant. Please read this letter carefully. Do not hesitate to ask anything about the information provided. Your doctor or nurse will describe the study and answer your questions.

Purpose

The rationale for this project focuses on preventing bleeding in total hip replacement surgery. The ability to stop bleeding is of concern to the surgeon, as joint replacement carries a high risk of complications when significant bleeding happens. Albeit necessary at times, and generally deemed safe, your surgical team is looking to decrease the rate of transfusion of blood products after your hip replacement.

Tranexamic acid is a drug that has received lots of attention recently, as it helps to reduce post-operative bleeding. In total knee replacement, a tourniquet around the leg can be used to control bleeding; this is not possible when your surgeon is operating on your hip. Currently at LHSC, tranexamic acid is administered in its intravenous (IV) form to most patients undergoing joint replacement. Your anaesthetist would give you this drug prior to the start of the operation.   This same drug placed directly into the joint (termed 'topical' administration) at the end of the procedure may also be beneficial; giving it this way allows for direct action of the drug on sites of bleeding. Compared to the IV route, there is less of the drug absorbed throughout the rest of the body. To date, no studies have directly compared IV versus topical administration of tranexamic acid in hip replacement surgery in terms of either safety or effectiveness.

This study is designed to compare the two methods of administering tranexamic acid in patients who receive a total hip replacement. The two groups studied are as follows:

1. One group will receive the intravenous form of tranexamic acid, administered prior to the start of the procedure. This is the standard protocol for joint replacement at University Hospital.
2. The second group will receive the topical form of tranexamic acid, to be infiltrated as a sterile solution directly into the hip joint once the implants are secured into the bone. It will be kept in for 5 minutes while your orthopaedic surgeon finishes the operation.

In order to provide further insight into the absorption of tranexamic acid, we will also collect one additional blood sample within one hour of administration of the drug, in both groups, to measure levels of tranexamic acid in the blood stream. All other blood samples will be drawn as per the standard hip replacement pathway. The investigators will collect data indicative of post-operative bleeding and any complication that arises during your stay in hospital.

The results from this study may help researchers improve blood conservation strategies for hip replacement surgery in the future. The main purpose of this study is to determine which route of administration provides the safest and most effective way of delivering tranexamic acid during hip surgery. If no difference is seen, the current standard of care, which is to administer the drug intravenously prior to the procedure, will continue to be utilized.

Approximately 144 patients from London Health Sciences Centre will participate.

Procedure

Should you meet the study criteria and wish to participate, you will be randomly assigned, like a flip of a coin, to one of the two groups. You will not know what group you are in. All patients will continue to receive the same level of care in the time leading up to, during, and after surgery.

Either during surgery, or while you are recovering from surgery, a health care professional will collect a blood sample to be sent for tranexamic levels.

After your surgery, the investigators will monitor your progress in hospital by reviewing your medical chart. Only data relevant to the study will be collected from your chart. A de-identification process ensures that only the study investigators will be able to link the health information contained in the chart with your personal information. The care providers that follow your progress after hip surgery will not be aware which study group you are in, and will not be able to answer questions related to the study. There will be no information present within your chart that tells the nurses and allied care professionals for of the drug you have received. However, the surgeon and residents caring for you while in hospital may be aware of which group you are randomized to, and are given strict instruction not to discuss the study or divulge any study-related information. They will determine whether you will need a blood transfusion, and will manage any medical issues

that arise while you are in hospital. There will be no difference in your hip replacement, physiotherapy or nursing care after surgery.

Study Risks

By participating in this study, you are at no increased risk compared to current standard of care in total hip replacement surgery.

As your medical chart will be reviewed, an infringement on your privacy may occur. Your individual results will be held in confidence. No person, other than your doctor, nurses and the study team will have access to your study-related records without your permission.

During the course of the study you will be informed of any significant new finding (either good or bad), such as changes in the risks or benefits resulting from participation in the study or new alternatives to participations that might change your decision to continue participating in this study. If new information is provided to you, your written consent to continue participating in this study will be requested.

Study Benefits

You may or may not benefit directly from participation in this study. The results of this study may be of benefit by helping surgeons discover new ways to reduce blood loss during hip surgery.

Voluntary Participation

Participation in the study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at anytime with no effect on your future care. You do not waive any legal right
by signing the consent form. There is a process of de-identifying your personal health information from the data collected in the study. Be aware that once data has been de-identified it will become impossible to have your data withdrawn from the study.

Alternatives to Study Participation

You will receive standard medical care by your doctor if you choose not to participate in this study. If you decide not to participate in this study, your surgeon and anaesthesiologist will determine whether or not you will receive tranexamic acid during your surgery. You do not have to participate in this study in order to have your hip replacement surgery.

Confidentiality

You will not be identified personally in any publication or communication resulting from this study. All

information collected will be stored in a locked office and entered into a secure database, accessible by authorized individuals only. Your identifiable information, such as your name, hospital identification number and surgery date, will be held separately from the other information collected and will be only linked by a study ID number. This information will be used solely for the advancement of medical science and any personal information will be kept confidential. A copy of this letter will be given to you.

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.
If you have any questions about your rights as a research participant or the conduct of the study you may contact Dr. David Hill, Scientific Director, Lawson Health Research Institute

If you have any questions about this study or your care please contact Katherine Hrabok, Clinical Research Coordinator, Department of Orthopaedics, London Health Sciences Center – University Hospital, or Dr. Jamie Howard, primary study investigator and Orthopaedic Surgeon at London Health Sciences Center.

Comparative Efficacy of Topical versus Intravenous Administration of Tranexamic Acid in Primary Total Hip Arthroplasty

Informed Patient Consent

Agreement of Participating Subject

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.

Print Participant's full name

Participant's signature   Date

Name of person obtaining consent

Signature of person obtaining consent   Date

Appendix D: Medical Directive for Tranexamic Acid

London Health Sciences Centre

SRG-2010-003

Medical Directive Title:	Preoperative Written Order for Tranexamic Acid (TA) in Orthopedic Surgery
Lead Contact Person:	Donna Berta, PBCP Coordinator
Program:	Surgery / Anesthesia and Perioperative Medicine
Approval By:	Medical Advisory Committee
Original Effective Date:	Revised Date:	Reviewed Date:

This Medical Directive Applies to: ☐ All LHSC sites   or

☒ LHSC-UH ☐ LHSC-VH ☐ LHSC-SSH

Order:
  Knee surgery:
      Send to Surgical Prep Unit
      Tranexamic acid * mg (wt ** kg), in 50 mL 0.9 % sodium chloride IV, administer at patellar clamping
       v/o Dr. F. Ralley/_____ PBCP RN

  Hip surgery:
      Send to Surgical Prep Unit
      Tranexamic acid * mg (wt **kg), in 50 mL 0.9 % sodium chloride IV, administer 10 minutes prior to
      skin incision
      v/o Dr. F. Ralley/_____ PBCP RN

*   dose of TA based on table Tranexamic Acid order per Patient Weight Increment (see Appendix 2)
** patient's weight measured at Preadmission Clinic assessment or estimate if patient unable to weight
   bear

Appendix Attached? ☒ Yes ☐ No

Recipient Patients:
University Hospital Orthopedic Surgery patients of Drs. Bourne, Howard, MacDonald, McAuley, McCalden, and Naudie assessed via Preadmission Clinic undergoing elective surgical procedures
- unicompartmental, primary, bilateral, revision knee joint replacement
- primary, bilateral, revision hip joint replacement
- periacetabular and femoral osteotomy and open surgical dislocation hip surgery

Authorized Implementers:

Position / Title	**Qualifications / Certifications**
Registered Nurse	RN in the Blood Conservation Program

Indications & Contraindications:
Indications:
1. All University Hospital Orthopedic Surgery patients assessed via Preadmission Clinic undergoing elective surgical procedures (procedures as listed **Recipient Patients**) provided the patient has absolutely no history of previous thrombotic vascular event (TVE)
2. For University Hospital Orthopedic Surgery patients assessed via Preadmission Clinic undergoing elective orthopedic surgical procedures not listed in **Recipient Patients,** if the PBCP nurse believes TA might be indicated, she may contact the attending Orthopedic Surgeon for direction regarding potential implementation of intra-operative TA

Relative Contraindications:
1. The PBCP Nurse will consult the PBCP Director or their designate regarding patients with history of TVE. The PBCP Director or designate will review such patients to assess the patient specific risk/benefit profile and advise the PBCP nurse if TA is to be ordered or not.
2. The PBCP Nurse will consult the PBCP Director or their designate regarding patients with drug eluting stents to treat coronary artery disease within the previous 2 years and ongoing Plavix treatment. The PBCP Director or designate will review such patients to assess the patient specific risk/benefit profile and advise the PBCP nurse if TA is to be ordered or not.

Absolute Contraindications:
1. Patients with history of TVE in previous 12 months or requiring life long anticoagulation related to previous TVE

Medication / Drug Table:

Drug Name (GENERIC only)	Route of Administration & Dosage Range	Indication	Absolute Contraindications	Considerations for Dosage adjustment (e.g. Renal or hepatic)	Special Monitoring Requirements (i.e. lab tests)
Tranexamic Acid	Intravenous in 50 mL 0.9 % sodium chloride minibag See Appendix 2 regarding dosage range Administered intraoperatively by Attending Anesthesiologist	To decrease surgical blood loss in orthopedic knee and hip joint surgery	Patients with history of TVE in previous 12 months or requiring life long anticoagulation related to previous TVE	none	none

Reference:

1. Compendium of Pharmaceuticals and Specialties. Canadian Pharmacists Association, Ottawa 2007:
    Cyklokapron, 649.
2. LHSC intranet Parenteral Drug Administration Manual
    http://www.lhsc.on.ca/priv/monograph/Of8oII6eAhQAABICTNE.htm

Consent:
- Attending Orthopedic Surgeon who obtains the surgical procedure consent, also obtains consent for blood and blood products and any alternatives (Form #8460-5645 revised 2008)

Educational Requirements
Information or educational requirements to guide practice include:
- Minimum of 5 years recent clinical experience in surgical patient care
- Completion of ONTraC blood conservation orientation program
- Ongoing participation in ONTraC program continuing education

Appendix attached? ☐ Yes ☒ No

Documentation & Communication:
- PBCP assessment, consultation with PBCP Director or their designate, plan of care and treatment implemented is documented on the patient's Health Record utilizing Perioperative Blood Conservation Program form (NSR5080 revised 2009).
- Written order for TA is documented on the LHSC Patient Care Order form (8460-5602 revised 2009)

Review and Quality Monitoring Guideline:
- For this Medical Directive TVE is defined as: stroke, transient ischemic attack, deep vein thrombosis, pulmonary embolism
- The PBCP director or their designate will be contacted via email (as per LHSC Electronic Mail Use Policy INT 006) regarding patients with history of TVE. The PBCP Director or designate will review such patients to assess the patient specific risk/benefit profile and will reply by email to advise the PBCP nurse if TA is to be ordered or not.

In situations of limited pre-operative time frame, telephone communication will occur

- All University Hospital Orthopedic Surgeons track their own patient TVE incidents; frequency of TVE incidents is reviewed semi-annually at Orthopedic Surgeons Division meeting. Dr. D. Naudie, Orthopedic Surgeon and PBCP Committee member will advise PBCP Director or their designate of any increase in frequency of such incidents
- Blood transfusion rates for University Hospital Orthopedic Surgery procedures are reported semi annually to the PBCP Director and to Orthopedic Surgeons by Donna Berta, PBCP Coordinator

Professional Staff Approvals (Physician, Dentist, Midwife):

- Identify all **Professional Staff members (<10 list by individual name, >10 list by title & program) responsible for patients who may receive an order or procedure under this medical directive.**

NAME	DEPARTMENT / PROGRAM
Dr. Fiona Ralley	Director, PBCP
Dr. Ian Chin-Yee	Hematologist, PBCP
Dr. Cyrus Hsia	Hematologist, PBCP

SRG-2010-003

Administrative Authorization Approval Form

Please note: signature pages are not to be signed until the medical directive has been approved.

Medical Directive: Preoperative Written Order for Tranexamic Acid (TA) in Orthopedic Surgery

Lead Contact Person (s):   <u>Donna Berta, PBCP Coordinator</u>

Administrative Authorizations (approved by):	Signature	Date
Chair, LHSC Medical Advisory Committee / Dr. Christopher Fernandes		
Chair, Drug & Therapeutics Committee / Dr. David Massel		
Director, Perioperative Blood Conservation Program / Dr. Fiona Ralley		
Hematologist, Perioperative Blood Conservation Program / Dr. Ian Chin-Yee		
City-Wide Chair-Chief Anesthesia & Perioperative Medicine / Dr. Davy Cheng		
Anesthesia Site Chief – University Hospital / Dr. Chris Harle		
Orthopedic Surgery Division Chief / Dr. James Roth		
Surgery Site Chief – University Hospital / Dr. Steven J. MacDonald		
Director, Surgical Care Program / Ms. Carol Rhiger		

Nursing Professional Practice / Kathleen Ledoux, or delegate		
Implemented by: (Person(s) performing initiation or person representing a large group and responsible for notification of that group)	**Signature**	**Date**
Donna Berta, PBCP Coordinator		
Valerie Binns, PBC Coordinator		

Appendix E: Copyright Permissions

Figure 1.2

Dear Rick

Thank you for your inquiry. Please find our permission statement below. This permission relates exclusively to this request:

Hardinge K. The direct lateral approach to the hip. *J Bone Joint Surg [Br]* 1982;64-B:17-19 (Figures 3, 4, 5 and 6)

Thank you for your permission request. We are pleased to grant permission for you to reproduce figures 3, 4, 5 and 6 from the aforementioned article, *provided full and correct acknowledgement of source is given*. On this occasion the permission is granted free of charge as permission is for inclusion in your Masters' thesis and therefore falls under the category of academic purposes, and is not for widespread or commercial publication or distribution, but please note that our fees are usually £100 *per* page or £55 *per* table or figure, meaning that this permission request would normally cost £220 GBP.

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If you have any further questions, please do not hesitate to contact me.

Kind regards,

Figure 1.3

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Portion	figures/tables/illustrations
Number of figures/tables/illustrations	1
Format	both print and electronic

Figure 1.7

Curriculum Vitae

Richard Peter Nadeau BMSc MD

Education and Employment

2011 – 2016   **Orthopaedic Surgery Resident (PGY4)** – Western University, London, Ontario.
London Health Sciences Center and St. Joseph's Health Care London

2013 – 2014   **Masters of Science in Surgery (Candidate)** – Western University, London, Ontario.
Departments of Surgery

2007 – 2011   **Doctor of Medicine** – Laurentian University, Sudbury, Ontario.
Northern Ontario School of Medicine

2003 – 2007   **Bachelor of Medical Sciences** – Western University, London, Ontario.
Honours Specialization in Microbiology and Immunology, with distinction

Research

Current Projects

2013   Nadeau R, Somerville L, Ralley FE, Howard JL, and Naudie DDR. **Tranexamic Acid Comparison in Hip Replacement (TeACH-R) Trial: A Prospective, Randomized Controlled Trial**. Thesis project for Masters of Science (Surgery) Graduate Studies Program.

Publications

2010   Elwood CN, Lange D, Nadeau R, Seney S, Summers K, Chew BH, Denstedt JD, and Cadieux PA. **Novel in vitro model for studying ureteric stent-induced cell injury.** *BJU Int*. 105(9): 1318-1323.

Presentations

2013   Nadeau R, Somerville L, MacDonald SJ, and Howard JL. **Activity Levels After Total Hip Arthroplasty Complication**. Presented at the 41st Annual JC Kennedy Orthopaedic Surgery Residents' Research Day, London, Ontario. Abstract submitted for presentation at the 2014 Annual Meeting of the Canadian Orthopaedic Association, Montreal, Quebec.

2012   Suh N, Nadeau R, and Grewal R. **Subacute Scaphoid Fractures: Factors Predictive of Successful Non-Operative Treatment.** Presented at the Annual Meeting of the Canadian Orthopaedic Association, Ottawa, Ontario.

2010   Nadeau R, Anderson RJ, Boyle D. **Sedation and Analgesia Protocols in a Community-Based ICU: Does Daily Tracking Improve Concordance?** Presented at the Northern Ontario Health Research Conference, Sudbury, Ontario.

Posters

2014   Nadeau R, Somerville L, MacDonald SJ, and Howard JL. **Activity Levels After Total Hip Arthroplasty Complication**. Presented at London Health Research Day (LHRD) and Dr. Robert Zhong Department of Surgery Research Day.

2013   Nadeau R, Stewart E, Lee T, Garvin G, Romano W, Faber KJ, Athwal GS, Drosdowech DS. **Imaging the Structural Bone Graft in Reverse Total Shoulder Arthroplasty.** Oral Presentation at the 40th Annual JC Kennedy Orthopaedic Surgery Residents' Research Day, London, Ontario. Poster presented at the Annual Meeting of the Canadian Orthopaedic Association in Winnipeg, Manitoba.