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Hand Swelling after Hand and Wrist Surgery: An Evaluation of its Effects and Assessment of Feasibility of a Double Blinded, Randomized Controlled, Pilot Study: Tranexamic Acid in Hand And Wrist Surgery (THAW) Study

Kendrick Au, *The University of Western Ontario*

Supervisor: Grewal, Ruby, *The University of Western Ontario*
: Ross, Douglas, *The University of Western Ontario*
: MacDermid, Joy, *The University of Western Ontario*
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Abstract & Key Words

Hand and wrist edema after surgery is a common side effect. It is often first identified visually by the treating physician or therapist. Once recognized, conventional edema treatment is typically partially successful. However, there are a subset of patients that continue to have significant postoperative hand and wrist edema following surgery despite these therapies. This can be devastating to the patient and may lead to pain, stiffness and a reduced quality of life. Surprisingly, there is limited research providing objective reference values for hand and wrist edema acutely after surgery. The first objective of this thesis was to objectively assess hand and wrist edema after commonly performed hand and wrist procedures. The second objective was to relate these data to commonly evaluated outcome metrics including pain, function and range of motion. The final objective was to evaluate the feasibility of a randomized controlled trial assessing the effects of tranexamic acid in hand and wrist surgery; a novel use of a medication that has shown promise in postoperative edema reduction.

Patients undergoing limited fasciectomy for Dupuytren's disease or open reduction and fixation for distal radius fractures were recruited over a three-month period. They were randomized to receive either a two-dose regimen of tranexamic acid or a placebo during the perioperative phase. Hand edema, patient reported outcomes, pain scores and range of motion data were assessed at multiple time points after surgery. Data analysis first assessed the entire cohort and then unblinded to assess for treatment differences. The limited fasciectomy cohort as a whole did not incur clinically significant hand and wrist edema throughout the postoperative phase. There were no correlations between edema and outcome measures in this group. Despite this, on average, patients had not recovered their full digit flexion by final follow up. The distal radius cohort had progressive decline of edema beginning at the first follow up. By the final follow up at three months, hand edema in this cohort had returned to near comparable values to the contralateral hand. This group showed a strong correlation between water displacement evaluation of hand edema and postoperative pain at multiple follow ups. The protocol used for this study proved to be feasible in obtaining the outlined objectives. A larger

clinical trial will be necessary to assess the effects of tranexamic acid in hand and wrist surgery.

Key words: edema, hand volume, Dupuytren's, limited fasiectomy, distal radius, feasibility, tranexamic acid

Summary for Lay Audience

Hand and wrist swelling ("edema") are common after hand and wrist surgery. Although many of the current available therapies are successful in preventing or reducing swelling, there are still a number of patients that suffer with swelling long after their surgery. If this happens, it can lead to pain and stiffness of the hand, which can often delay or prevent patients from returning to work and normal activities. Surprisingly, there is very little evidence that explains how the hand and wrist swells early after surgery. Our study first looked at the current evidence available and reviewed how hand and wrist edema forms, how it is tested in the clinical setting and how it is typically treated. From there, we investigated and unveiled new data that describes the normal course of hand and wrist edema after some common hand and wrist procedures. We also looked at the connection between the amount of swelling and other factors such as pain, stiffness and satisfaction.

After we studied how the hand and wrist normally swells after surgery, we investigated the effects of a drug called Tranexamic Acid (TXA) on hand swelling after hand and wrist surgery. This drug has been shown to decrease swelling in other areas of the body but has not been studied in hand and wrist surgery. In our study, patient's undergoing hand or wrist surgery were recruited to participate. The patients that qualified for the study were randomly assigned to either receive TXA or a placebo. A patient's hand volume was measured and compared to values obtained before and after surgery. This was a small study that collected data to evaluate if a larger study with more patients is possible. Therefore, the goal was to make sure the process of the study does not need modifications before starting a larger trial. It also helped identify any trends that deserve more attention in future studies.

Co-Authorship Statement

Chapter 1:
Sole Authorship: Kendrick Au
Manuscript Review: Dr. Ruby Grewal, Dr. Joy MacDermid, Dr. Douglas Ross

Chapter 2:
Study Design: Kendrick Au, Dr. Ruby Grewal, Dr. Joy MacDermid, Dr. Nina Suh
Data Collection: Kendrick Au, Dr. Ruby Grewal, Katrina Munro, Christina Ziebart
Data Analysis: Kendrick Au, Dr. Ruby Grewal
Statistical Analysis: Kendrick Au
Manuscript Preparation: Kendrick Au
Manuscript Review: Dr. Ruby Grewal, Dr. Joy MacDermid, Dr. Douglas Ross

Chapter 3:
Sole Authorship: Kendrick Au
Manuscript Review: Dr. Ruby Grewal, Dr. Joy MacDermid, Dr. Douglas Ross

Acknowledgements

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CHAPTER 1: Introduction

The purpose of this thesis was to quantify acute hand and wrist edema following commonly performed hand and wrist surgeries. These reference data were used to assess the relationship of edema to postoperative outcomes and to evaluate the feasibility of a study investigating a new therapy that may prevent or decrease postoperative hand and wrist swelling. This chapter focuses on providing an overview of the current literature as it pertains to hand and wrist anatomy, edema physiology and formation, current trends in edema treatment and a review of tranexamic acid – a drug that is investigated in future chapters. Finally, the rationale, objectives and thesis hypothesis are reviewed.

1.1 RELEVANT ANATOMY

The wrist and hand are comprised of an intricate network of structures that function seamlessly and in symphony to achieve complex, daily functional demands. Basic tasks like hand pinch, grasp and grip all necessitate joint stability, fortified musculotendinous units, adequate tendon gliding and pliable skin.[1] The wrist joint is a complex coalition of multiple joints that are categorized into the radiocarpal, midcarpal and carpometacarpal joints. Further distally, the three main joints of the fingers are the metacarpophalangeal (MCP) joint, proximal interphalangeal (PIP) joint and distal interphalangeal (DIP) joint. Under standard conditions they have a complementary relationship that propels the normal arc of motion of the wrist and fingers. However, digital stiffness after trauma or surgery can alter these mechanics resulting in dysfunction of neighbouring joints and digits.[2] An understanding of the relevant anatomy is imperative to comprehend the pathological process of stiffness and to effectively advance it's treatment.

1.1.1 The Wrist and Carpus

The wrist consists of the distal end of the radius and ulna, eight carpal bones and the proximal bases of five metacarpal bones. The carpal bones are organized into two rows - one proximally and one distally. These rows are between the distal end of the

1

radius/ulna and proximal bases of the metacarpals. The proximal row is an intercalated segment; meaning there are no tendon insertions and the collective motion is solely dependent on the surrounding articulations. The distal carpal row is tightly bound by stout ligaments, with minimal motion between them. The ligaments of the wrist are generally categorized as intrinsic or extrinsic ligaments. Intrinsic ligaments exist within the carpal row while extrinsic ligaments cross between the various levels of the wrist and carpus (Figure 1). These ligaments function to provide a stable link for this complex network of bones. Joint capsule, surrounding tendons and soft tissue structures also play a secondary role in wrist and carpal stability. Wrist and finger flexor and extensor tendons primarily have a role in motion of the hand and wrist. At the wrist, these tendons facilitate flexion, extension and lateral bending (also known as radial and ulnar deviation). Wrist rotation is achieved mainly through a separate joint between the radius and ulna. It has been suggested through biaxial wrist electrogoniometry that roughly 70% of the maximum range of motion of the wrist is needed for the majority of daily function; specifically, this has been shown to be 60 degrees of extension, 54 degrees of flexion, 40 degrees ulnar deviation and 17 degrees of radial deviation.[3] For composite motion like pronation and supination, the functional range has been shown to be 100 degrees evenly divided between them.[4] Surgical trauma can lead to reduced mobility through the formation of edema in some of these critical areas. Consequently, the ligaments, tendons and joint capsule can become stiff and contracted leading to prolonged postoperative wrist and finger stiffness, perpetuated edema and reduced range of motion.
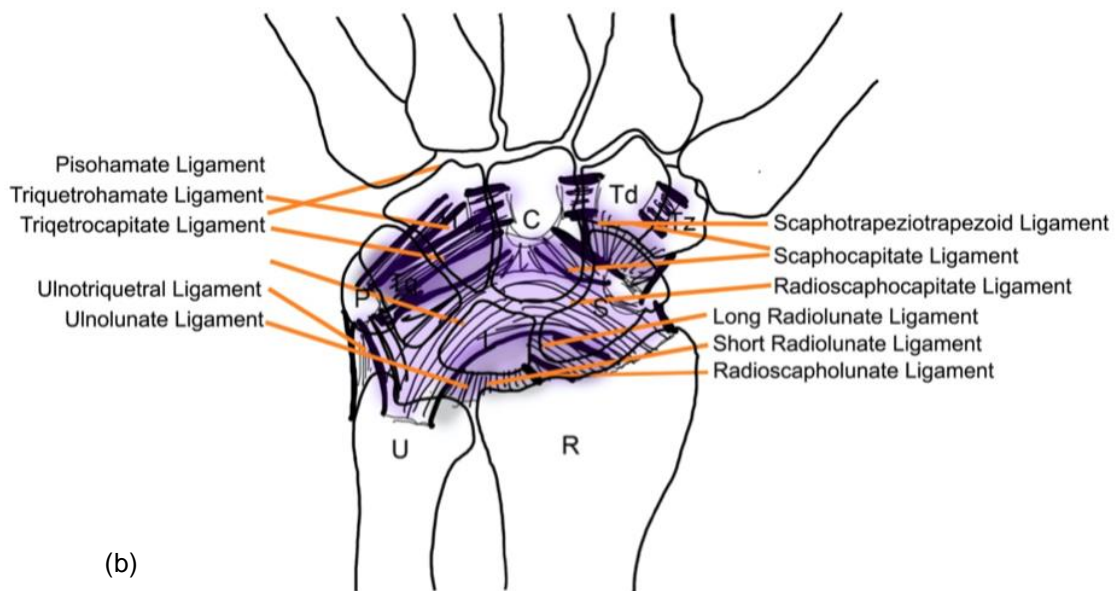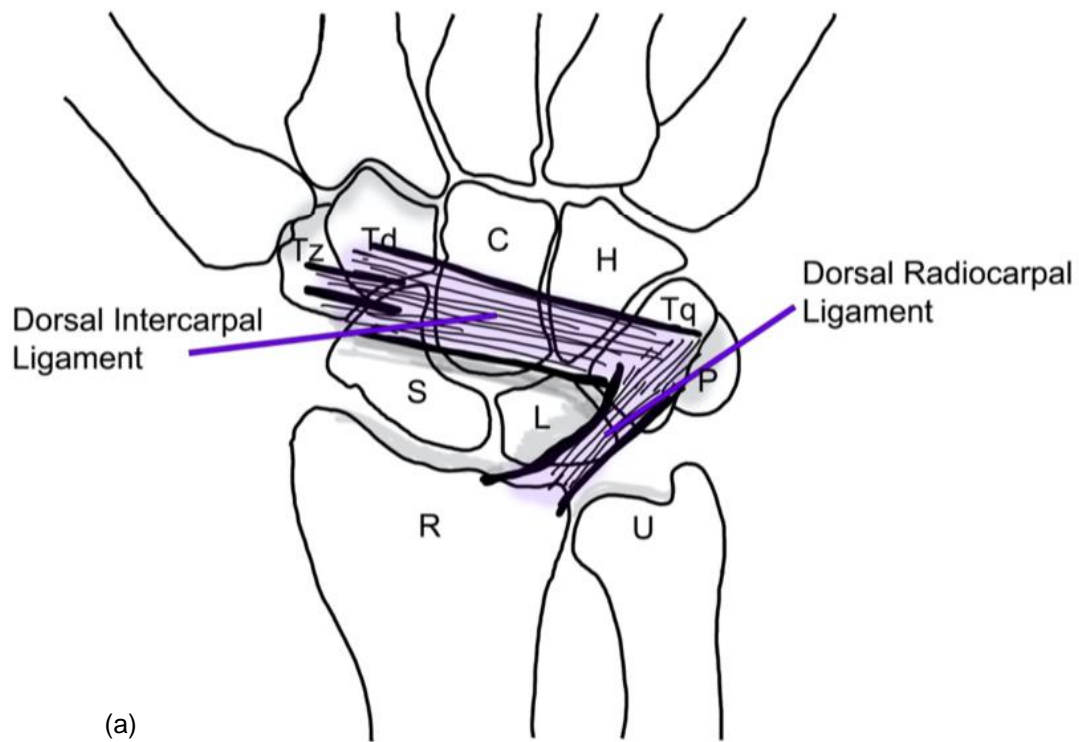
Figure 1: Relevant (a) dorsal and (b) volar extrinsic and intrinsic ligament structures of the hand and wrist. (Reused with permission from Mistry, MR. 4DCT analysis of in-vivo carpal kinematics during FEM. The University of Western Ontario; 2022. https://ir.lib.uwo.ca/etd/8227)

1.1.2 The MCP Joint

The MCP joint is a multiaxial condyloid joint made up of the proximal phalanx and metacarpal head. The multiaxial component allows for multi-planar movement: flexion/extension, abduction/adduction and a small amount of circumduction. The normal arc of motion of the MCP in the sagittal plane ranges from slight hyperextension to 100 degrees of flexion. A study measuring functional range of motion of common daily living tasks evaluated 35 patients using electrogoniometry. They found that the average functional arc of motion of the MCP joint was 61 degrees (range 33-73 based on the task).[5] The main components of the MCP joint include the joint capsule, two proper collateral ligaments, two accessory collateral ligaments and the volar plate (Figure 2). The joint capsule has built-in redundancy to allow a variable amount of hyperextension of the proximal phalanx, distraction and a small degree of rotation. It is stabilized by connective tissue on all sides as it is attached to the articular rim of the metacarpal head and the base of the proximal phalanx.[1] The volar plate is a thickened portion of the volar capsule, functioning as a checkrein against MCP hyperextension and an attachment site for the collateral ligaments The two proper collateral ligaments originate from the radial and ulnar subcapital area of the dorsal metacarpal head, coursing towards it's attachment on the volar base of the proximal phalanx. The accessory collateral ligaments originate slightly proximal and volar to the proper ligaments on the metacarpal head and fan out to blend into a uniform ligament, inserting on the volar proximal phalanx and volar plate. The length of the collaterals elongate as the joint goes from an arc of extension into flexion.[6] Their predominantly dorsal origin is eccentric to the axis of rotation and thus creates a cam effect on the proximal phalanx as its flexed. As such, MCP joint flexion produces tension in the collateral ligaments and provides maximum joint stability. The collateral ligaments are maximumly stretched at 70 degrees of flexion.[7] Conversely, the collateral ligaments are lax in extension. If in the setting of postinjury, or postsurgical edema, the MCP joint assumes an extended posture for a significant period of time, it can lead to shortening of the collateral ligaments, scarring of the capsule and stiffness of the joint.[2]
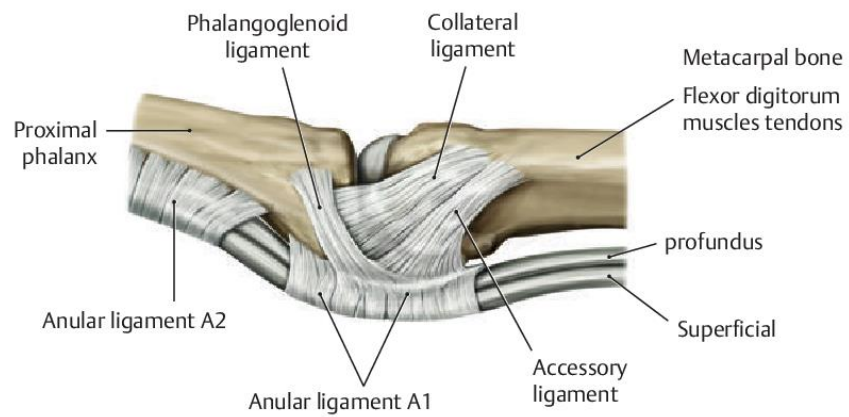
Figure 2: Diagram of a lateral projection of the MCP joint, depicting the osseous and soft tissue structures about the metacarpophalangeal joint. (Reused with permission from Elsevier publishing. Hirt et al, Hand and Wrist Anatomy and Biomechanics. Annals of Anatomy. Vol 211, May 2017. doi.org/10.1016/j.aanat.2017.01.004)

1.1.3 The PIP Joint

The PIP joint is a single axis hinge comprised of the proximal phalanx and base of the middle phalanx. The joint moves purely in the flexion-extension plane. The arc of motion generally is between slight hyperextension to 110 degrees of flexion.[2] The median functional arc for the PIP joint was found to be 63 degrees.[5] The volar plate of the PIP has proximal expansions on either side of the volar plate proper. These extend to the volar margins of the proximal phalanx and attach to the periosteum. These are commonly referred to as checkrein ligaments; they are unique to the PIP joint and limit hyperextension (Figure 3). Similar to the MCP joint, the PIP joint has 2 proper collaterals and 2 accessory collaterals. However, unlike the MCP joint there is no CAM effect resulting in uniform tension of the ligaments throughout the arc of motion. The collateral ligaments and volar plate create a three-dimensional (3D) ligament box that plays a major role in PIP joint stability. In additional contrast to the MCP joint, the PIP joint tends to develop a flexion contracture due to the functional overpull of the more powerful flexor tendons. Volar plate contracture, shortening of the checkrein and collateral ligaments and contracture of the flexor sheath all contribute to a chronic PIP flexion contracture.[8]

(a)

(b)
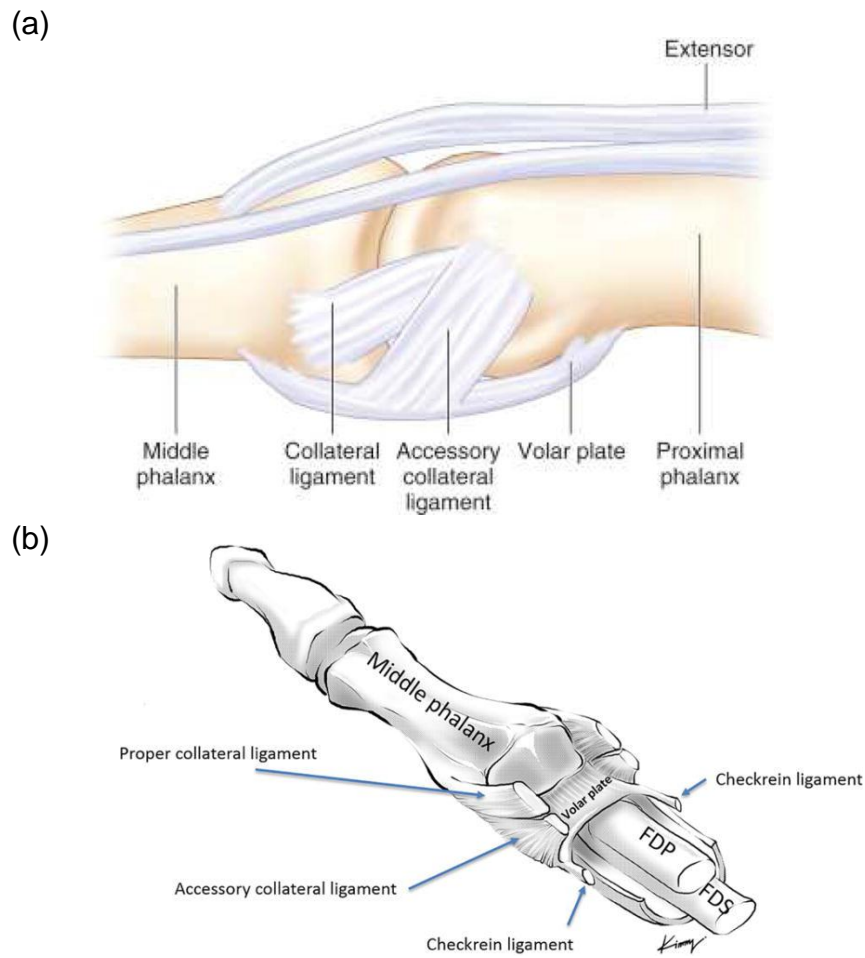
Figure 3: (A) Anatomy of the soft tissue stabilizers of the PIP joint. (B) A 3-sided box analogy commonly used to describe the volar, radial and ulnar restraints of the joint. (Reused with permission from Elsevier publishing. Kamnerdnakata et al, Complications of Proximal Interphalangeal Joint Injuries: Prevention and Treatment. Hand Clin 34 (2018) 267–288. https://doi.org/10.1016/j.hcl.2017.12.014)[9]

1.1.4 The DIP Joint

The DIP joint, comprised of the middle and distal phalanx, also has a single axis of motion of flexion and extension. The adjacent soft tissue stabilizers are similar to the proximal joints, with the addition of the terminal tendon attachments which provide accessory support.[1] The normal range of motion of the DIP is 0 to 85 degrees, while it has been demonstrated that the median functional arc is 39 degrees (Figure 4).[5]
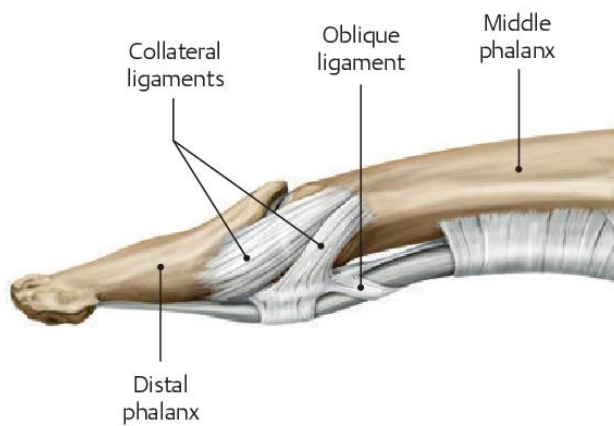
Figure 4: Anatomy of the osseous and soft tissue structures of the DIP joint. (Reused with permission from Elsevier publishing. Hirt et al, Hand and Wrist Anatomy and Biomechanics. Annals of Anatomy. Vol 211, May 2017. doi.org/10.1016/j.aanat.2017.01.004)

1.2 FORMATION OF HAND EDEMA

Edema refers to the presence of excess extracellular fluid in body tissue. When edema occurs in the hand, it can infiltrate the tendon sheaths, ligaments, capsule and synovial spaces.[10] If it persists, this can lead to limitations in motion and ultimately delay return to activity. To understand this process, it is helpful to review the basics of fluid exchange at the cellular level.

1.2.1 Physiology

All cells are bathed in extracellular fluid which can be divided into two main components: the interstitial fluid and the blood plasma.[11] The interstitial fluid is outside of the closed vascular system, while plasma is the suspension fluid for circulating red blood cells, white blood cells and platelets. Under normal conditions, the exchange of fluid occurs through diffusion and filtration. This occurs between tissues and circulating blood at the level of the capillaries. The net filtration of fluid across the capillary is influenced by the force of fluid that is pushed out into the interstitial space (filtration pressure) versus the forces that move fluid inward (resorption pressure). These forces, known as Starling forces, are generally placed in two broad categories: the force of the diffusion of water, also known as hydrostatic pressure and the force induced by proteins known as colloid osmotic pressure. Classically, Starlings equilibrium theory states that the hydrostatic pressure inside the capillary at the arteriole end tends to be higher than in the interstitial space, resulting in diffusion of fluid and dissolved substances into the interstitial space.[12] Conversely, colloid osmotic pressure in plasma at the level of the venules tends to be higher than in the interstitial space drawing fluid from the interstitial space back into the capillary by osmosis.[12,13] Under this model, the overall filtration pressure is slightly greater than resorption pressure resulting in roughly 90% reabsorption of the filtrate from the capillary back into the venous system.[13] However, Starling's model of equilibrium has since been modified. The discovery of a separate endothelial layer on the luminal surface of vessels, known as the endothelial glycocalyx layer (EGL) has challenged the notion of an increased capillary oncotic pressure gradient causing venous reabsorption (Figure 5).[14] This layer absorbs albumin from the

plasma and contributes significantly to the total intravascular colloid oncotic pressure. Therefore, the oncotic gradient actually exists between the EGL and intravascular space, limiting overall reabsorption from the interstitial space.[14] Consequently, this modification implies that the main route of return for fluid is actually through the lymphatic system.

The lymphatic system influences the volume of interstitial fluid and resultant pressure by pulling excess fluid and proteins out of the interstitial space, into the lymphatic system (being relabelled as lymph); eventually lymph is deposited back into to the general circulation through this pathway. However, during surgery the EGL can be become disrupted. This can lead to endothelial dysfunction, an increase in protein escape and an increase in capillary filtration, resulting in a bolus of fluid movement into the interstitial space.[15] Although the contents of the interstitial space can swell up to 30-50% to accommodate increased interstitial free fluid, beyond 50% can overwhelm the lymphatics leading to dynamic insufficiency edema.[11] Importantly, this can then impair the natural diffusion process of waste and nutrients, putting patients at risk for delayed healing, infection, skin breakdown and cell damage.
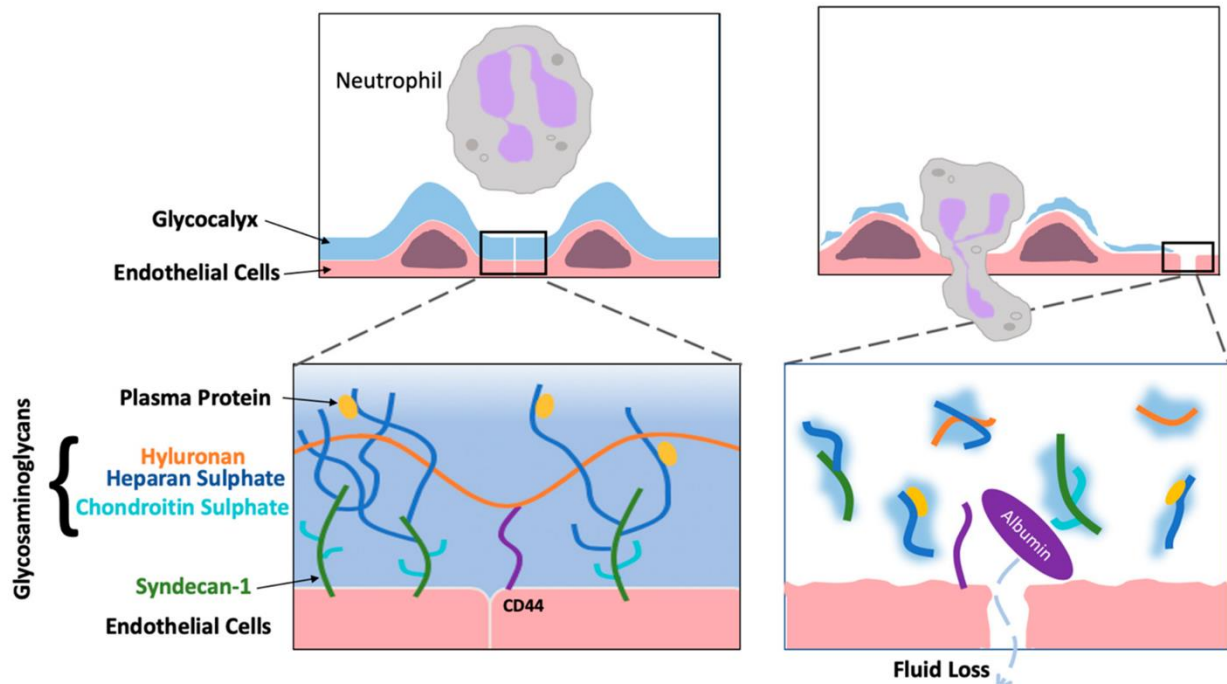
Figure 5: EGL structure during health (left) and degradation (right). Disease causes thinning of the glycocalyx. (Reused under open access Creative Common CC BY license. Kahn et al, Protective Treatments against Endothelial Glycocalyx Degradation in Surgery: A Systematic Review and Meta-Analysis. *Appl. Sci.* 2021, *11*(15), 6994; https://doi.org/10.3390/app11156994)

1.2.2 Post-surgical Edema Stages

Post-surgical edema occurs in three stages: inflammation, fibroplasia and maturation.[16] The first 3-5 days is known as the inflammatory phase. During this early time in wound healing, most wounds will have excess fluid. Chemical mediators are released which initially cause vasoconstriction, followed by vasodilation. There is a natural release of histamine and bradykinin from tissue injury that causes an increase in tissue permeability – allowing passage of fluid and white blood cells through the cell walls to form plasma. Debris is cleaned, and fibrinogen is converted to fibrin. At this stage edema is quite easy to mobilize, with a soft consistency. Small amounts of edema can be managed by the lymphatic system, but excessive amounts may overwhelm the system inhibiting wound healing by decreasing arterial, venous and lymphatic flow and increasing diffusion distance.[16]

The fibroplasia phase follows the inflammatory phase and is also commonly known as the proliferative phase. Aptly named, it encompasses processes such as increased capillary growth, increased fibroblast production, new collagen synthesis, fibrin deposition and accelerated scar production. Collagen is a normal and major component of all soft tissues, making up 77% of all fat-free dry weight.[17] In normal circumstances, joint motion promotes collagen formation that meet functional requirements. The forces that act across the joint are critical to determine the quantity, alignment, length and structural organization of newly formed collagen fibers. Eventually, the crosslinking that occurs help fortify the collagen structure while allowing for maximum elongation, permitting full joint range of motion in the process. However, pain and edema after a surgical or traumatic insult, can inhibit motion. Under this environment, new collagen will form in a shortened, disorganized fashion.[18] The additive effect of this progressively disorganized meshwork is tightening and shortening of pivotal anatomical structures such as tendons and tendon sheaths, collateral ligaments, joint capsule, synovial membrane and fascial layers.[18–20] Edema at this phase has a higher protein content (known as exudate) and consequently is more viscous. If the lymphatics are still burdened at this stage, dynamic insufficiency will also ensue.[16]

Beyond the fibroplastic phase, the maturation phase occurs. At this stage adhesions and restrictions in range of motion are firmly established and difficult to modify. The stagnant edema at this phase is quite hard, thick and brawny as a result of connective tissue infiltration and fibrosis. In addition, there remains a relatively high concentration of proteins in the interstitial space which increases the capillary net filtration pressure – drawing even more fluid in. As this continues, tissue exudate creates a sluggish environment for fluid transport. In turn, normal pressures are no longer sufficient for adequate fluid removal. This further impairs nutrition exchange, forming brawny edema in the spaces around injured cells.[16]

1.3 CLINICAL EVALUATION OF HAND

The assessment of hand edema is an important clinical evaluation that can provide valuable, longitudinal feedback to the patient, physician and therapist over the course of management. As edema lingers and enters the maturation phase, it becomes more challenging to mobilize, leading to persistent stiffness and deficits in range of motion. With accurate, reproducible methods of quantifying edema, a clinician can use this information to help monitor and adjust the rehabilitation process. The available clinical techniques for edema evaluation range from subjective visual inspection to more objective measures such as water displacement, Figure-of-Eight measurements, three-dimensional techniques, bioimpedence spectroscopy (BIS) and more regional measurements such as finger circumference or ring gauge techniques. Most clinical studies have used these clinical tools in the subacute phase of hand edema.[21] Surprisingly, limited literature exists regarding the quantification and evolution of acute edema directly after surgery.

1.3.1 Visual inspection

Visual inspection is a common method of evaluating edema in the clinical setting. It is fast and inexpensive but is subjective and generally arbitrarily assigned. To improve accuracy, formal documentation should be based on hand colour, tautness of the skin and visibility of defined anatomical landmarks.[22] A standardized grading scale should then be used for final determination. Even if using a standardized approach, the varying perceptions of severity amongst clinicians and as well as the lack of an agreed upon standard grading scale across physicians and therapists limits the usefulness of this method on its own. A study assessing 88 patients with post-stroke hand edema evaluated the agreement between visual inspection (rated as nil, minor or severe) and the gold-standard objective measurement, water displacement.[23] They found that there was only a 67% agreement between classification of edema and the volumeter. Sensitivity and specificity analysis showed that visual inspection was only 76% sensitive and 63% specific. Consequently, this suggests visual inspection should be combined with a more objective measurement technique for accurate assessment of hand edema.

1.3.2 Water Displacement

The water displacement method has been used since the 1950's and is the referenced gold standard for measuring hand edema. The concept of the water displacement method is based on Archimedes' principle and laws of buoyancy, which states that the volume of displaced fluid by an object is equivalent to the volume of that object fully immersed in a fluid (Figure 6). It involves the use of a volumeter – an enclosed container that has an overflow spout allowing for displaced fluid to pour into a collection beaker for eventual measurement. Prior to testing, the volumeter is filled with tepid water to a consistent level. Once zeroed, the patient lowers their hand into the water with the palm facing their abdomen. There is a dowel located in the volumeter which acts as a marker for standardizing depth for contralateral hand and subsequent measurements. The patient is instructed to lower their hand until the bottom of their third webspace (the space between the ring and long finger) contacts the dowel. The water flows out of a spout and is collected in a beaker and the measurement is completed once all droplets stop from the overflow spout (Figure 7). The total volume is measured in a graduated cylinder in millilitres (mL). Based on the work by Waylett-Rendall et al, a difference of 10mL with a normal hand and 12mL in an edematous hand is considered indicative of significant change in tissue volume.[24] Water temperature should remain consistent to improve reliability and is generally recommended to be at room temperature (68-95°F); as the use of warmer water has been shown to increase the volume in asymptomatic hands.[25,26] Testing can be performed with the patient seated or standing; however, the same position should be used for all measurements.[27] This method has an excellent track record for reliability and validity, and has a margin of error of less than 1%. A systematic review of 15 studies using the water displacement method showed the intertester reliability was generally good to excellent (ICC=0.74-0.99), intratester reliability was good to excellent (ICC=0.83-0.99) and test-retest reliability was excellent (ICC=0.99).[28] Measurement variability calculations ranged from 1.6-12.6 mL with a single tester and 1.0-22.0mL when measured by more than 1 tester. As such, relative variations were <1.2% when measurements were taken by a single tester, and <17.7% when more than one tester was used.[28] Although the water displacement method offers a high fidelity technique of measuring hand edema, it does

come with some disadvantages. There is an added upfront cost associated with the volumeter kit, it is often discouraged with the use in open wounds and there is added time involved with its setup, which can be impractical in busy clinic settings.
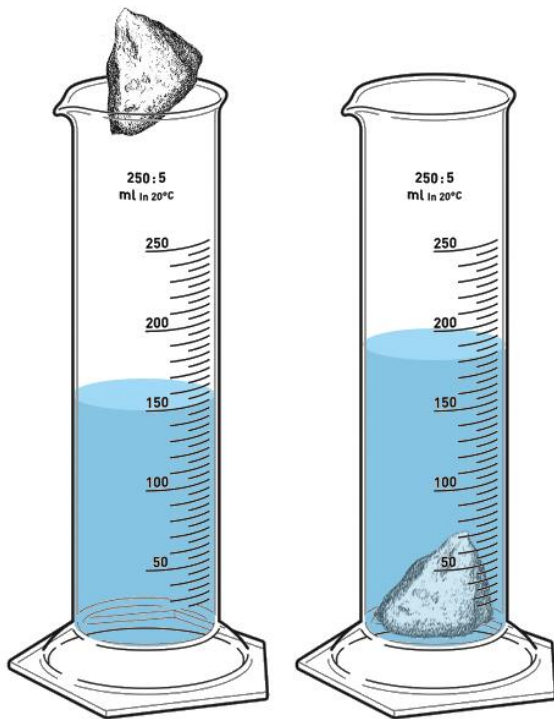
Figure 6: Archimedes' principle law of buoyancy (Reused under the Creative Commons Attribution-Share Alike 4.0 International. Belbury et al, Displacement Measurement. https://commons.wikimedia.org/wiki/File:Displacement_measurement.png)
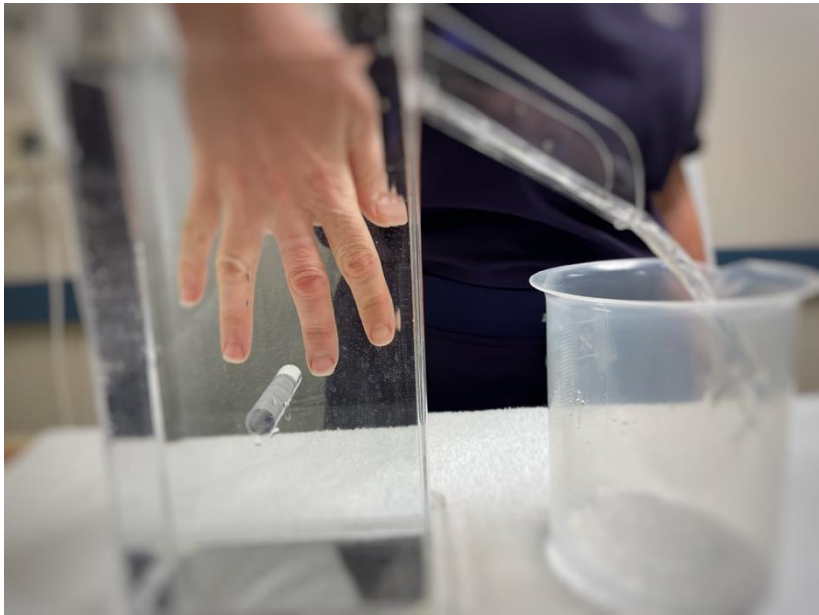
Figure 7: Water displacement method

1.3.3 Figure-of-Eight Method

The Figure-of-Eight method of measuring hand volume offers a simplified approach to hand edema measurement. A standard, non-stretch tape measure is used to pass around reference landmarks over the hand and wrist, forming a Figure-of-Eight pattern (Figure 8). The values are a representation of the global size of the hand and are presented in centimeters or millimeters. Based on intertester standard error from the evaluation of 24 patients with conditions affecting the hand, Leard et al concluded that measurements should differ by 0.56cm to be considered indicative of true change in hand size.[29] Outcomes of Figure-of-Eight measurements have been compared to water displacement for validity and reliability. The volume outcomes produced showed moderate to very high association with the reference technique (r = 0.70-0.96). The inter- and intratester reliability were both good to excellent (ICC=0.84-0.99, ICC=0.86-0.99). Measurement error by a single rater ranged from 2.6-7.1mm and a similar range was found for multiple testers (2.8-6.0mm).[28] The variable laxity on different tape measurers can lead to altering results, especially in edematous hands, where excessive tension can displace edematous tissue. As such, standardised protocols and repetitive practice are vital for accurate, reproducible results.

Figure 8: Figure-of-Eight method.

1.3.4 Three-Dimensional Imaging Techniques

Three-dimensional imaging techniques include the use of a perometer, laser scanner or stereophotgrammetry. These techniques use emitted light or cameras to capture data points and calculate volumes using non-disclosed algorithms. Intra- and intertester reliability for these methods are all excellent with the ICC ranging from 0.95-0.99 and can be used in patients with open wounds or injuries. Despite this, there are some inherent disadvantages to these techniques. For example, the accuracy of a perometer may be adversely affected with incorrect limb position. This is especially true in patients that do not have hand swelling. When a hand is swollen it has a reduction of interdigital air spaces and has more of a triaxial ellipsoid shape. However, in a hand without swelling there is a portion of air within the interdigital space even in a tightly held position. In this situation the perometer can still view the hand as an elliptical object and erroneously include the air within its calculation. In an evaluation by Lee et al, the use of a perometer showed inter- and intrarater reliability that was lower for the sub-group of twenty women without lymphedema than those with; it systematically overestimated hand volume by a mean of 24mL compared to a volumeter.[30] Despite its high reliability compared to reference standard volume measurements, because of this calibration issue it has been suggested that these methods not be used interchangeably.[22] Although it is easy to use and patient-friendly, the associated cost of these technologies has also hindered its widespread implementation.[22,31]

1.3.5 Bioimpedence Spectroscopy (BIS)

Bioimpedence Spectroscopy (BIS) is a measurement technique that uses a low-frequency current to measure the ECF volume of the palmar and dorsal regions of the hand. The tissues' resistance to the current reflects the volume of ECF in the designated space and generally is compared to the contralateral hand. This is useful for swelling conditions such as lymphedema where there is a surplus of ECF volume. It has excellent intertester reliability (ICC=0.94-0.97) and highly correlated to perometer readings in comparison.

1.3.6 Regional Assessment

Regional assessment of swelling can be accomplished by finger circumference or ring gauge methods. The finger circumference method involves sizing of the affected finger at the level of the proximal phalanx using a non-stretch tape measure. A torque meter or device formed by a ruler and cloth strap wrapped around the middle finger can be implemented to provide feedback for consistent tension applied on the tape measure during measurements.[32] Both inter- and intratester reliability were good to excellent (ICC=0.88-0.95, ICC=0.98-0.99).[28,32–34] However, outcomes of this method have not been compared against a criterion reference to assess validity. The ring gauge method involves the use of a set of rings to evaluate the size of the finger at the level of the proximal phalanx. The smallest ring to fit at the proximal end of the finger is identified and the finger size is calculated on a scale from 0-30. Each size on the scale correlates to a specific diameter in millimeters. When compared to finger circumference, the ring gauge method was highly associated with finger circumference measurements and maintained excellent inter- and intratester reliability.[28]

1.3.7 Factors Influencing Hand Volume Measurements

The various nuances associated with each measurement technique require close attention to ensure proper standardization and accuracy. There are also a number of other factors that can cause variability of hand volume that should be kept in mind during the measurement process. Van Velze et al studied the effect of hand dominance on hand volume in 263 male laborers and found that on average the nondominant hand was 3.43% smaller than the right dominant hand.[35] Aging can also alter skin texture, permeability and vascular properties of the hand. Siamwala et al found that the change in hand volume after 20 mins of water immersion was larger for the younger patient population (<40 years old) when compared to an older cohort.[36] There is also a physiologic temporal component to hand swelling as shown by Warrender et al.[37] In their study, they found a significant increase (average of 4.5%) in hand swelling in patients during the nocturnal hours of 8PM to 8AM, with a trend towards hand volume reduction during the remaining hours of the day. Activity level has also been shown to increase hand volume. It has been demonstrated that women's hand volumes increased 3.6% immediately after exercise, while men's hand volumes increased by 5.2%, with a decline at time intervals post-exercise.[38] As such, changes pre- and post-exercise would need to be greater than 25mL to account for this expected increase in hand volume with exercise.[38,39] Overall, it is important to account for these potential variables during the measurement and analysis process in order to ensure accurate results.

1.4 CURRENT TREATMENT OF ACUTE HAND EDEMA

The prevention and treatment of edema in the hand and wrist is critical to maximize functional return after surgery or injury. Often this involves prophylactic treatment before edema is even measurable. There have been a number of different modalities described across the literature, limiting the ability for a proposed consensus on appropriate methods, dose response and duration of a "standard" intervention.[21] Nevertheless, it is agreed upon that edema prevention and management within the first two phases is vital to optimizing range of motion and patient outcomes. In the acute inflammatory stage ice, elevation, compression and appropriate early motion should be instituted to prevent escalation to prolonged edema. If edema persists into the fibroplasia phase additional techniques to stimulate the lymphatic system may be required.

Overall, there is a breadth of current modalities used to treat edema. Synthesis of the current evidence suggest that a combination of these various interventions may be best in providing prevention and treatment. However, the quality of the evidence and variability of treatment create limitations in providing concrete recommendations or a standardized algorithm. In addition, despite the use of these modalities there still exists a subset of the population that progress to the chronic phase – a stage that is more difficult to treat and resulting in worse overall outcomes. As such, there is an opportunity for improvement in the prevention and early treatment of postoperative hand edema based on the current literature.

1.4.1 Cold Therapy

Cold therapy can be applied in a variety of different manners - continuous ice water, cold immersion, cold gel packs and cryopress. It can produce vasoconstriction, reduce the metabolic rate and reduce the arteriolar blood flow. In theory, this should reduce membrane permeability and capillary infiltration resulting in a reduced flow of proteins and fluid into the interstitial space. In practice, although there have been many studies that have demonstrated a decrease in edema after the use of various cold modalities compared to standard therapy,[40–43] the question of sustained benefit after sessions remains. To maximize benefit, it has been suggested by some authors that cold therapy be used in combination with other principles of edema management such as elevation, compression or electrical stimulation.[44–46] Cold therapy should be used with caution in the case compromised vascular status, such as arterial repairs or vascular disease.

1.4.2 Elevation

Elevation is another tactic used in the early inflammatory phase to decrease edema. It's mode of action utilizes gravity to enhance venous and lymphatic outflow. Overall, this reduces hydrostatic pressure in the blood vessels which decreases capillary filtration pressure at the arterial end. Alternatively, when the hand is below the level of the heart, the intravascular pressure is increased. This increases capillary filtration pressure causing interstitial fluid to accumulate in the dependent hand.[16] In clinical practice, this is a common recommendation to patients, however, the evidence is limited. Fagan et al randomized forty-three patients undergoing a carpal tunnel procedure to high elevation at home or sling treatment. Volumetric analysis of the hands on postoperative day five did not show a statistical difference between the two groups.[47] It has also been shown that the benefits of elevation may in fact be transient. Tsang et al reviewed twelve subjects with ankle sprains, randomizing their treatment to either elevation alone or elevation and intermittent compression. They found a significant difference in ankle volume between the pre-treatment and immediate post-treatment for both cohorts. However, these effects dissipated in both groups only five minutes after the limb was returned to a gravity dependent position.[48] The evidence suggests that elevation alone is not a sufficient method of edema reduction and should be used as an adjunct with other therapies.

1.4.3 Compression

Compression is another strategy for edema prevention; it reinforces the hydrostatic pressure of tissues and facilitates venous and lymphatic flow. In the acute phase it is considered to reduce the amount of space available for swelling to accumulate. As edema persists into the fibroplastic phase, compression is believed to decrease fibroblast synthesis by decreasing blood flow and causing local hypoxia – in essence slowing down scar tissue formation. Intermittent pneumatic compression has also been described as it increases hydrostatic pressure, accelerating lymphatic and venous flow, facilitating return of lymph to the venous system. However, it has mixed results in lymphedema and hand therapy. Segers et al showed wide discrepancies between the target pressure set by a control and the actual pressure delivered (actual pressure delivered was up to 80% higher than the control).[49] It should also be used with caution in the initial management of edema as it can cause additional bleeding.[16]

1.4.4 Lymphatic Drainage

Manual lymphatic drainage is a technique employed to increase the efficiency and frequency of lymphatic vessel contraction. Lymphatic massage has been shown to increase the frequency of lymphatic vessel contraction, thereby increasing the transport capacity of the system. In the inflammatory phase, lymphatic drainage can be instituted with a focus proximal to the site of insult. This enables stimulates the downstream lymphatics and helps pull fluid proximally without creating additional inflammation distally. In the fibroplastic phase, stimulation of the lymphatic system is crucial in order to encourage proteins to move from the interstitial space into the lymphatics.[16] However, some studies suggest that the benefits of this therapy may diminish over time once active treatments cease.[50]

1.5 TRANEXAMIC ACID (TXA)

22Tranexamic acid (TXA) is a medication that inhibits fibrinolysis, or the breakdown of stable clots. It has been used as an antifibrinolytic in surgical disciplines for decades to reduce intraoperative blood loss and consequent transfusions. Recently, studies in other surgical disciplines like plastic surgery and otorhinolaryngology have also demonstrated a reduction in postoperative edema.[51–56] Although the use of TXA in hand surgery has not been extensively studied, these latest findings spark intrigue in its additive role in the prevention of postoperative hand edema.

1.5.1 Mechanism of Action

The mechanism of action of TXA exists within the complexity of the coagulation cascade. To review, the fibrinolytic system is an integral part of vascular hemostasis and functions to ensure vascular patency during a steady state.[57] At its core, the pathway involves the conversion of the inactive substrate of plasminogen to its active form plasmin – an enzyme that functions to cleave fibrin into fibrin degradation products. Fibrin is the active form of fibrinogen, which is the key component of clot formation. Simply put, plasmin is responsible for breaking down a stable clot and fibrin is responsible for creating one. Plasmin has also been shown to trigger the proinflammatory pathway of the complement system. This involves a mediated release of vasoactive peptides such as bradykinin and histamine which increases tissue permeability and allows passage of fluid through the cell walls to form plasma, resulting in a proinflammatory environment.[58] This is a tightly regulated system under normal conditions, with a variety of activators and inhibitors functioning to safeguard hemostasis. Plasmin can be generated by endothelial activation, release of tissue plasminogen activator (tPA) or urokinase plasminogen activator (uPA) and by contact activation with kallkrein-mediated plasmin activator. To balance, plasmin generation is hindered by multiple inhibitors such as plasminogen activator inhibitor 1, thrombin-activatable fibrinolysis inhibitor and alpha2-antiplasmin (Figure 9).[59–61] The equilibrium is altered, however, with the introduction of tissue injury in trauma or surgery. The increase in plasmin production and subsequent fibrinolysis that occurs at this stage is

thought to be an important contributor to bleeding, coagulopathy and a proinflammatory response.[62]

TXA is a lysine analog that acts as a competitive antagonist on plasminogen. Plasminogen has five binding sites for TXA, one with high affinity and the remaining ones with low affinity.[63] In effect, it's binding prevents activation of plasmin and obstructs fibrinolysis (Figure 10). Additively, without active turnover to plasmin and resultant fibrin degradation products, TXA may also reduce the proinflammatory effects that have been described.[58] Interestingly, *ex-vivo* studies seem to indicate that TXA may have either a proinflammatory or an anti-inflammatory effect through the complement cascade. Barrett et al suggested that the proinflammatory protein C5a, from the complement system, was either upregulated or downregulated by TXA based on the predominating plasminogen activator present. If uPA-mediated plasmin was predominant, TXA increased levels of C5a, while with tPA-mediated plasmin TXA decreased levels of C5a.[64] This mixed effect of TXA adds to the dichotomy of proinflammatory effects described by both fibrin and fibrin degradation products.[65] Despite this, TXA is also thought to have a protective effects on the endothelium and has been shown to render beneficial modulation of inflammation and other responses following ischemia and reperfusion.[65,66]
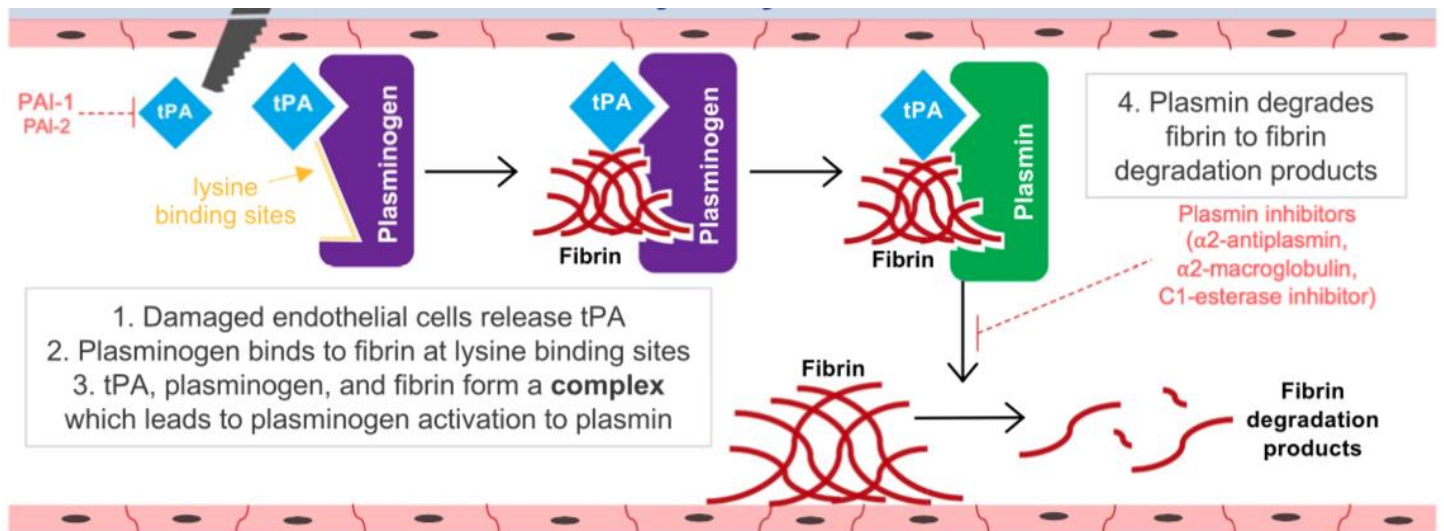
Figure 9: The fibrinolytic system (Reused under open access under http://creativecommons.org/licenses/by-nc-nd/4.0/ License. Relke et al, Tranexamic acid evidence and controversies: An illustrated review, Res Pract Thromb Haemost. 2021 Jul; 5(5): e12546. doi: 10.1002/rth2.12546)
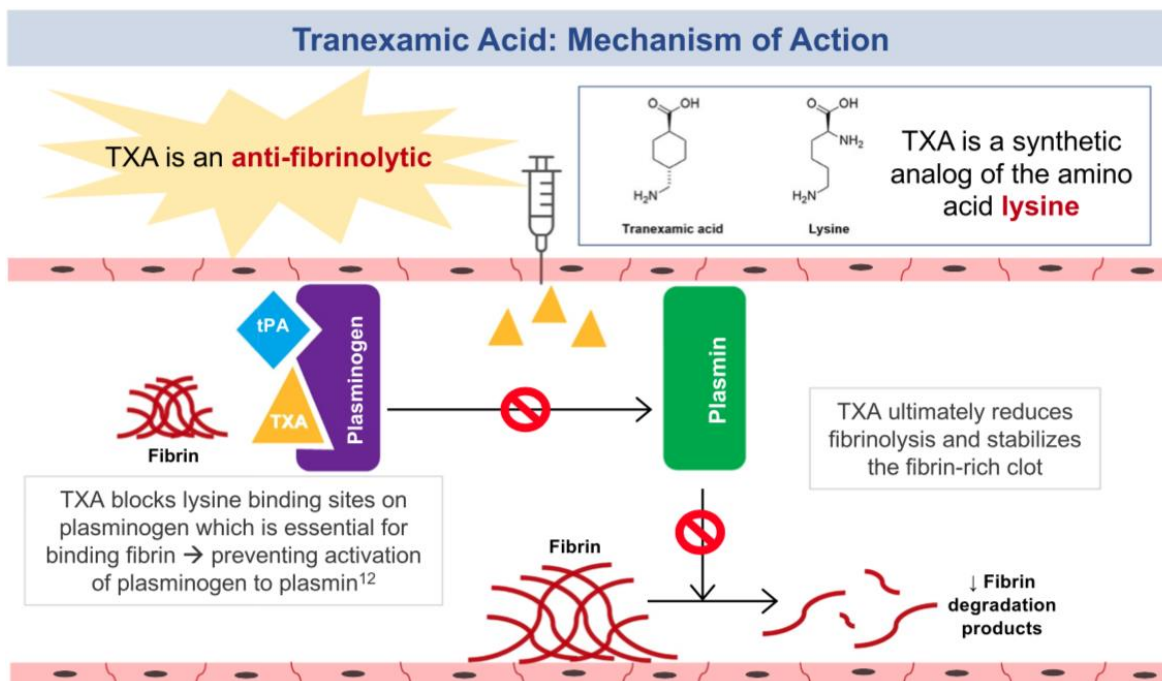
Figure 10: The mechanism of tranexamic acid (Reused under open access under http://creativecommons.org/licenses/by-nc-nd/4.0/ License. Relke et al, Tranexamic acid evidence and controversies: An illustrated review, Res Pract Thromb Haemost. 2021 Jul; 5(5): e12546. doi: 10.1002/rth2.12546)

1.5.2 Route of Administration

The approved indications for the use of tranexamic acid vary among countries. In many countries, it is approved for the treatment of bleeding or during increased local fibrinolysis.[67] Although the most common route of administration for tranexamic acid is intravenous, alternative described methods include topical, oral (tablets or solution), intramuscular, nebulized and intraosseous.[54,68,77–79,69–76] Injectable forms of the medication are generally used for more rapid delivery situations such as surgery or trauma, while topical, oral or nebulized formats are typically reserved for other indications. The use of topical therapy as an alternative to intravenous therapy in surgery has been studied and shown to be successful for clinical scenarios where systemic absorption is less desired.[80,81] In addition, it's use as an adjunct to intravenous therapy in certain surgical disciplines has shown a trend of improved efficacy.[77,71,82]

1.5.3 Surgical Dosing, Administration and Pharmacology

The ideal dose of tranexamic acid is based on the desired outcome to of inhibiting fibrinolysis. Recently, a systematic review evaluated both *in-vitro* and *in-vivo* studies reporting the relationship between TXA concentration in blood or plasma and reliable measures of fibrinolysis. Of the 21 studies meeting the inclusion criteria, 20 of them were *in-vitro*. The synthesis of these studies showed that TXA concentrations between 10 to 15 mg/L resulted in substantial inhibition of fibrinolysis, while lower concentrations of 5 to 10 mg/L were also partly inhibitory. To date, the minimal effective plasma concentration of TXA to effectively induce fibrinolysis based on an *in-vivo* dose-response relationship has not been determined.[83] Ergo, the dosing of TXA in the clinical setting remains largely empirical. This has been reflected in the breadth of intravenous dosing regimens reported; this has ranged from a standard 1-gram intravenous dose to weight-based dosing. A systematic review of the effect of TXA on surgical blood loss demonstrated a drug total range of 5.5 to 300mg/L across 104 trials.[84] Interestingly, a meta-regression from this study suggested that the effect of TXA on blood loss did not vary over these dose ranges.[84] When using a fixed dose of TXA, Franz et al showed no difference in blood product administration in patients <100 kilograms (kg) versus those that were ≥100kg.[85] These studies would suggest fixed dosing strategies are sufficient in inducing a desired inhibition of fibrinolysis, however, the variability amongst an abundance of literature prohibits formal dosing guidelines. Regimens including post-bolus infusions or multiple doses have also shown mixed results and recommendations for these dose schedules remain inconclusive.[86–93] A prospective randomized trial by Iwai et al compared a single pre-incision IV dose of TXA with an additional dose 3 hours after the operation in total knee arthroplasty patients and found a lower drain output postoperatively in those who received the 2 doses (p<0.001).[94] Likewise, Maniar et al compared different IV regimens and found a significant reduction in total blood loss and drain output in patients who received a 3 dose schedule (preoperative, intraoperative and postoperative) compared with those that had a single or double dose.[95] As TXA's effect on fibrinolysis is dose dependent, it is possible that number of doses and timing may impact the clinical effects of TXA. Despite these results, this concept has not been reflected in larger, higher level review studies.[96]

In surgery, tranexamic acid can be administered prior to skin incision, during the operation around the time of tourniquet deflation and/or postoperatively. The current available data remains inconsistent on defined recommendations. Those favouring early administration advocate TXA works most effectively early in the fibrinolytic cascade. Even with tourniquet use, pre-incision TXA dosing has been shown to be just as effective as intraoperative administration.[96,97] Alternatively, the argument for TXA administration prior to tourniquet release[89,91] is that it may be more effectively and efficiently delivered to the injury site.[98]

Once administered, the peak plasma concentrations of intravenous TXA are obtained rapidly, and diffuses quickly into the synovia, joints and other tissues.[99,100] Tranexamic acid does cross the placenta, producing cord blood concentrations similar to maternal plasma concentrations. However, concentrations of TXA in breast milk have been found to be only about 1%. In addition, TXA does cross both the blood-brain-barrier, producing cerebrospinal fluid and aqueous humour concentrations that are about 10% of plasma levels.[101] From a single 1g intravenous dose, plasma concentrations $\geq$10mg/L can be sustained for up to 5-6 hours, with a half-life of 2-3 hours.[101] Oral and intermuscular administration results in rapid absorption with peak plasma concentrations at 2-3 hours and 0.5 hours, respectively. The systemic bioavailability of oral and intermuscular TXA is estimated to be about 33-46% and 100%, respectively.[73,101] Plasma concentrations decline in a multiexponential manner and the majority is eliminated unchanged in the kidneys via glomerular filtration; it is excreted in the urine within 2 to 3 hours after administration.[99,100] With a 10mg/kg IV dosing regimen, about 30% of the drug is recovered in the urine within 1 hour, while 90% of a single intravenous application is eliminated by 24 hours.[99,100-101] A dose adjustment for those with glomerular function deterioration is recommended, although optimal dosing remains unknown.[99,102] Since only a small proportion of administered TXA is metabolized, dose adjustment for hepatic impairment is not necessary.[101]

1.5.4 Safety and Contraindications

The risk of thrombosis with the use of TXA has been a topic of controversy. In theory, TXA has prothrombotic properties and therefore could put patients at risk for thromboembolic events. However, published results have been variable ranging from no incidence of a thromboembolic event[103] to a 12-fold increase in DVT with the use of IV TXA.[104] A criticism of many published studies is that they often exclude patients with major comorbidities, potentially underrepresenting the higher risk cohorts. Yates et al in a systematic review and meta-analysis of 268 eligible studies showed a relative risk of a venous thromboembolism (VTE) from systemic TXA to be 0.97 (95% confidence interval, 0.99-1.22) in studies that excluded patients with prior thromboembolic disease. Whereas, studies that did not apply this exclusion found a risk of 0.89 (95% CI, 0.63-1.27) for VTE. Although this may indicate it could be as safe to use in this cohort, further direct comparative studies are needed to conclude safety given the wide range of confidence intervals. In addition, the study also concluded that systemic TXA did not significantly increase the risk of an adverse event compared to placebo or no intervention based on 224 studies that reported adverse events (RR 1.05, 95% CI, 0.99-1.12).[105] Although there was no statistical significant increase in the risk of adverse events in using TXA in this study, the presented confidence interval should also produce caution in concluding TXA's safety given the current evidence. Taeuber et al has added some supportive evidence in their systematic review of 216 trials encompassing 125,550 patients. They found an overall rate of thromboembolic events of 2.1% in the TXA groups and 2.0% in the control groups (calculated RR=0.95), with no statistically significant difference between the two groups (p=0.49). This study also was unable to find any correlation between an increase in TXA dose and increased thromboembolic events.[106]

TXA also acts as a competitive antagonist of $GABA_A$ and glycine receptors. An increased binding of TXA to these receptors can decrease inhibitory current and increase excitability, potentially lowering the seizure threshold. Most seizures have been reported in patients undergoing "open chamber" cardiac surgery, but there have been

some case reports of in other patient cohorts.[107–109] The incidence of seizure has a cumulative risk of 2.7%; however, there is a significant dose-effect correlation with higher doses (>80-100mg/kg total) having an increased risk. Other risk factors include cardio-pulmonary bypass surgery time >150min, renal dysfunction, age >75 years and poor overall health.

Canadian guidelines for TXA use include contraindications of an active or past history of thrombosis, subarachnoid hemorrhage, hypersensitivity, hematuria, patients on anticoagulants and disturbances in colour vision. The US Food and Drug Administration (FDA) have also recommended excluding women on oral contraceptive. Given the increased risk of a venous thromboembolism with the use of an oral contraceptive, there is a theoretical concern that TXA will further increase this risk. However, the World Maternal Antifibrinolytic (WOMAN) trial suggests combination is safe; they did not find an increased risk of venous thromboembolism (VTE) in post-partum woman (hormonal effects similar to OCP).[103] Although no harmful effects have been reported, the safety of TXA during pregnancy has not yet been fully established.[67]

1.5.5 TXA: Select Landmark Trials

The antifibrinolytic effects of TXA were first published in the 1960's, with its empiric administration advocated for liver transplantation. However, it was the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial in 2013 that stimulated awareness of TXA among specialties leading to its mainstream use.[110] This trail randomized 20,211 adult trauma patients with or at risk of significant bleeding in 274 hospitals across 40 countries. The patients were randomly assigned to receive TXA within 8 hours of injury (1g loading dose over 10 minutes then an infusion of 1g over 8 hours) or a placebo (normal saline). The TXA cohort showed a reduction in all causes of mortality within 28 days (an absolute risk reduction of 1.5% and a number needed to treat of 67) and death due to bleeding (absolute risk reduction of 0.8% and a number needed to treat of 119). A second publication from this study reported on a subgroup analysis on those that died specifically from bleeding. This analysis demonstrated that early application of TXA within 1 hour after trauma was associated with the largest benefit (2.4% absolute risk reduction, number needed to treat of 41).[110] An extrapolation of this data showed that TXA had the potential to save between 70,000 – 100,000 lives each year, leading to its addition to the World Health Organizations (WHO) list of "Essential Medicines" in 2012.[111,112] Subsequent to the CRASH-2 trial, another large trial followed, investigating the role of TXA in postpartum hemorrhage (PPH). The World Maternal Antifibrinolytic (WOMAN) trial investigated the effect of TXA compared to placebo on death due to bleeding in PPH patients.[103] The WOMAN trial demonstrated a small but statistically significant reduction in death due to bleeding in patients who received TXA (NNT = 250), particularly if the dose of TXA was given within 3 hours of delivery and in those patients requiring a laparotomy for bleeding control (NNT = 220).[103] A follow up study by the CRASH-2 group compared the administration of 1g IV TXA or placebo within 3 hours of traumatic brain injury in 9,202 patients (CRASH-3 trial).[113] They found a 1.3% reduction in all head-injury related death in the TXA group compared placebo. As an oral medication, TXA has also shown positive patient outcome scores in adult women with heavy menstrual bleeding. La et al showed in a randomized controlled trial of 187 patients with mean menstrual blood loss of ≥

80mL that a regimen of 1.3 g PO TXA TID was superior to placebo in improvements of health-related quality of life (p<0.01).[114]

However, TXA has not been shown to be universally effective. A large, randomized controlled trial of 12,009 adult patients with significant upper or lower gastrointestinal (GI) bleeds did not show a reduction in mortality with the use of IV TXA compared to placebo. The study did find a higher rate of VTE and seizures than other regimens; however, the study cohort had a higher average age than the CRASH-2 study (58 years vs 35 years), increased comorbidities and a higher level of liver disease (baseline decrease in fibrinolysis may be associated with increased VTE).[115,116]

Overall, these landmark trials provide a small lens of studies that have investigated the use of tranexamic acid on a large scale. These trials have inspired curiosity of the role of TXA in other disciplines and as a result, TXA has been one of the most reported pharmaceutical agents in the literature over the last decade.[117] This proves consistent in the writer's home discipline of Orthopaedic surgery. There are a plethora of trials outside the realm of hand and wrist surgery evaluating the effects of TXA ranging from postoperative blood loss to postoperative range of motion.

1.5.6 TXA Use in Orthopaedic Surgery

To date, the use of TXA in orthopaedic surgery has mostly been limited to investigating the effects on blood loss. A 2017 meta-analysis included twelve orthopaedic trauma studies assessing the efficacy of TXA on reducing blood transfusion and blood loss, while also assessing the difference in thromboembolic events.[118] Combined analysis demonstrated the that when patients were given TXA, there was significantly less risk of transfusion (a combined odds ratio of 0.407, p <0.001), significantly less blood loss (304mL, p<0.001) and no difference in thromboembolic events. Similar findings have been exhibited in joint replacement surgery. Independent network meta-analysis of total hip arthroplasty and total knee arthroplasty showed similar, strong parallel findings for the use of TXA in this subspecialty. The use of TXA in the topical, oral or intravenous form were all superior when compared to placebo for blood loss and risk of transfusion – while no formulation was clearly superior. Repeat or higher dosing in either hip or knee arthroplasty did not show a reduction in blood loss or risk of transfusion.[96,119]

A meta-analysis evaluating TXA in shoulder and elbow arthroplasty found four randomized controlled trials and five retrospective cohort studies that met criteria for review of shoulder arthroplasty but none were identified for elbow arthroplasty.[120] The authors found TXA administration correlated with a significant decrease in estimated blood loss (mean difference -358mL), postoperative blood loss (mean difference -113mL), change in hemoglobin (mean difference -0.71 g/dL) and total hemoglobin loss (mean difference -35.3g) when compared to placebo. In addition, the retrospective cohort studies also found a shorter length of stay associated with TXA use. Higher level research is needed to conclude the effect of TXA in total elbow arthroplasty, however.

In addition to the primary effect on blood loss, other orthopaedic subspecialties have found effects of TXA use on secondary outcome measurements. Separate meta-analysis of topical TXA in spine surgery and IV use in hip fracture treatment both showed a reduced length of stay compared to placebo or no intervention in addition to a reduction in blood loss.[121,122]. Dorweiler et al evaluated postoperative range of motion of

174 patients (75 controls and 99 receiving TXA) in a retrospective analysis of patients undergoing a total knee arthroplasty. They discovered patients who received TXA had an improved range of motion compared to the control group.[123] A systematic review of seven randomized controlled trials in arthroscopy surgery (knee, hip and shoulder) found a significantly lower hemarthrosis grade, improved operative visualization and a decrease in visual analogue pain scores (VAS) of pain at two weeks postoperatively in the TXA groups.[124] Additionally, a randomized controlled trial of 96 patients undergoing open elbow arthrolysis by Cui et al found a significant improvement in VAS pain scores in the first two postoperative days along with a decrease in total estimated blood loss and postoperative drainage volume with the use of TXA compared to placebo.[125] Hurley et al also showed that patients undergoing shoulder stabilization surgery demonstrated a significant improvement in postoperative swelling and hematoma formation (4% vs. 32%, $p < 0.01$), improved pain scores (1.7 vs. 3.0, $p < 0.01$) and diminished opioid use (9.4mg vs. 22mg, $p < 0.01$) in those treated with TXA compared with placebo.[126] These studies in orthopaedic surgery suggest supplementary benefits of TXA outside of reduced surgical blood loss. Specifically, the benefits of reduced pain scores, reduced joint swelling and improved range of motion adds to the recent body of literature on its potential role in edema management.

1.5.7 TXA Use in Edema Management

Tranexamic acid has been used as an on-demand and prophylaxis treatment for angioedema since the 1970's.[127] Angioedema is an autosomal dominant disorder most commonly due to a deficiency in C1 esterase, a protein of the complement system. It is characterized by recurrent episodes of localized subcutaneous or submucosal edema in the extremities, face, genitals, trunk and abdomen, lasting upwards of 2-5 days.[128] Laryngeal edema is potentially life threatening and can occur at any time point during the episode.[128] Tranexamic acid blocks the activation of the complement cascade by inhibiting plasmin formation, therefore provides a role for treatment in angioedema (Figure 11). Cumulative evidence of its use since the 1970's showed that it is not an effective solo therapy for on-demand treatment but has had some success in short-term and long-term prophylaxis of angioedema.[129]

The use of TXA for curbing postoperative edema and ecchymosis in surgical specialities has also shown promising results. A systematic review and meta-analysis of 332 patients across five randomized clinical trials in the field of plastic surgery, investigated the effects of TXA on intraoperative blood loss and postoperative edema among patients undergoing primary elective rhinoplasty. Their analysis showed significant reductions in facial edema and ecchymosis in three out of the five studies and an average decrease in blood loss of 41.6mL with the addition of TXA compared to the controls (p = 0.004).[130] Interestingly, two of the studies in this meta-analysis also used corticosteroids in addition to tranexamic acid. The subgroup analysis from these studies showed that tranexamic acid was superior to controls but was not superior to corticosteroids alone or when used in conjunction.[131,132] These results are consistent in other surgical studies for nasal surgery and septorhinoplasty. Two recent systematic review and meta-analyses in otorhinolaryngology surgery demonstrated that perioperative TXA successfully reduced edema and ecchymosis for both nasal and rhinoplasty procedures, while potentially reducing intraoperative blood loss and improving the quality of the surgical field.[133–135] These surgical studies further support the potential for TXA outside of its traditional use. The recent evidence in early edema

reduction, better pain scores and improved range of motion is the inspiration for the subsequent feasibility trial investigating TXA as a potential adjunct in hand surgery.
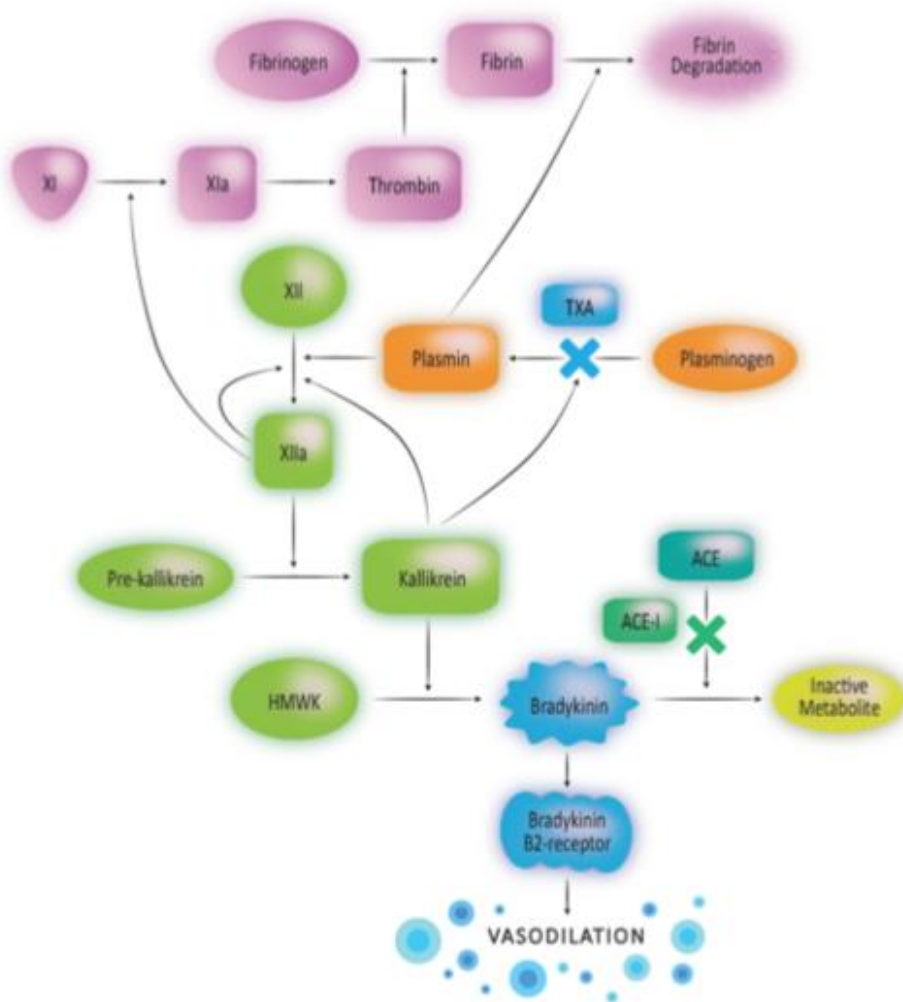
Figure 11: Tranexamic acid's mechanism in the reduction of vasodilation (Reused with permission from Elsevier publishing. Wang et al, Tranexamic acid for ACE inhibitor induced angioedema – A case report. American Journal of Emergency Medicine (2020), https://doi.org/10.1016/j.ajem.2020.10.029)

1.6 THESIS RATIONALE

Anatomy of the hand and wrist is complex and detailed. When healthy, it affords stability and motion to perform the necessary tasks of daily living. However, surgery in this area may cause swelling and diminished range of motion. If it persists, it may lead to devastating outcomes including stiffness, prolonged rehabilitation and diminished function.[50,136] These factors can reduce a patient's quality of life; mounting to an overall delay in recovery, return to work and daily activities.[21]

Clinically, there are tools to aid in the assessment of hand edema and allow clinicians and therapists to evaluate the effectiveness of treatment. However, little has been published regarding the natural course of hand swelling in the acute postoperative phase. Conventional edema therapy includes cold therapy, elevation, external compression, active and passive exercises and various types of massage.[11,16] Despite the best efforts of the hand therapist and patient, there still remains a subset of the population that develop chronic edema and stiffness.[21] Once hand edema becomes chronic, treatment becomes more challenging and outcomes more unpredictable. Consequently, there is much focus on optimizing treatment to prevent the overall formation of edema.

Tranexamic acid (TXA) is an antifibrinolytic that has been used in surgical disciplines for decades to aid in reducing intraoperative blood loss and consequent transfusions.[57] Recently, the use of TXA for curbing postoperative edema and ecchymosis shown promising results in head, neck and facial surgery; however, its use in hand surgery has not been studied.[137]

The purpose of this review was to discuss the relevant anatomy and physiology, evaluate current therapies for hand edema, review the mechanism of tranexamic acid and assess the body of literature surrounding TXA in surgery. The remaining aspects of this thesis was aimed to add to the existing literature surrounding postoperative hand edema. Specifically, we advanced our understanding of hand edema in the acute phase

after hand and wrist surgery. The reliability and validity of our clinical assessment of hand edema was scrutinized. Lastly, we evaluated the effects of TXA as it relates to postoperative hand edema and range of motion - a novel use of this medication. The feasibility of this protocol was assessed to outline the possibility and modifications needed to complete a larger randomized controlled trial using TXA in hand and wrist surgery.

1.7 THESIS OBJECTIVES

The primary objectives of this thesis were:

1. To objectively define acute hand and wrist edema after surgery

2. To assess the relationship of acute postoperative hand and wrist edema with clinical and patient reported outcome measures

3. To evaluate the feasibility of a randomized controlled trial involving tranexamic acid in hand and wrist surgery

1.8 THESIS HYPOTHESIS

The hypotheses of this thesis based on the objectives were:

1. Hand and wrist edema will initially increase after surgery and steadily fall at subsequent follow ups. Patients will still have residual swelling at the last follow up at three-months

2. There will be a correlation between postoperative swelling and the outcome scores. Increased swelling will be correlated with increased pain, reduced function and decreased range of motion.

3. The protocol set forth in the thesis to investigate tranexamic acid in a randomized controlled trial will be feasible to utilize as a template for a larger clinical trial.

Chapter 2: Hand Swelling after Hand and Wrist Surgery: An Evaluation of its Effects and Assessment of Feasibility of a Double Blinded, Randomized Controlled, Pilot Study: Tranexamic Acid in Hand And Wrist Surgery (THAW) Study

[NB: A portion of this material was presented in Chapter 1. It is also included here in order to ensure that this chapter is in "article" format].

Abstract

Introduction: *Hand and wrist edema after surgery is a common side effect. Surprisingly, there is limited research providing objective reference values for hand and wrist edema acutely after surgery. When clinically recognized, conventional edema treatment is typically partially successful. However, there are a subset of patients that continue to have significant postoperative hand and wrist edema following surgery despite these therapies, leading to pain, stiffness and a reduced quality of life. Tranexamic acid is an antifibrinolytic that has traditionally been used in surgery to reduce blood loss, but recent evidence indicates it may have potential in postoperative edema reduction. The main objectives of this study were to assess hand and wrist edema after commonly performed hand and wrist procedures, to relate these data to commonly evaluated outcome metrics including pain, function and range of motion and to evaluate the feasibility of a randomized controlled trial assessing the effects of tranexamic acid in hand and wrist surgery; a novel use of a medication.*

Methods: *Patients undergoing limited fasciectomy for Dupuytren's disease or open reduction and fixation for distal radius fractures through a volar approach were recruited over a three-month period. They were randomized to receive either a two-dose regimen of intravenous of tranexamic acid (one-gram) or a placebo during the perioperative phase. Hand edema, patient reported outcomes, pain scores and range of motion data were assessed at multiple time points after surgery. Data analysis assessed the entire cohort for trends and correlations of hand edema to clinical and patient reported outcomes. The feasibility of the protocol was assessed with predefined objectives.*

Results: *Fifteen patients in the Dupuytren's cohort and eight patients in the distal radius group met inclusion criteria. The limited fasciectomy cohort as a whole did not incur clinically significant hand and wrist edema throughout the postoperative phase (a mean maximum percentage 1.4%, SE 1.1 and maximum absolute of 8.8mL, SE 6.0). Patients trended toward improved PRWHE scores compared to baseline at the final follow up, but it did not reach a clinical important difference (19.2 vs. 7.1). There were no correlations between edema and outcome measures in this group. Despite this, on average, patients had not recovered their full digit flexion by final follow up (2.5cm, SE 0.4). The distal radius cohort also did not produce a surge of edema postoperatively (preop 15.5% vs. week two 9.0%) when using water displacement. There was*

progressive decline of edema and improvement of PRWHE scores beginning at the first follow up. This group showed a strong correlation between water displacement evaluation of hand edema and pain from the PRWHE at preoperative (r=0.77) and week 2 (r=0.84). The protocol used for this study proved to be feasible in obtaining the outlined objectives. An average recruitment for the Dupuytren's and distal radius group per month was five and three patients, respectively. There was an 80% adherence to protocol and retention rate in the Dupuytren's cohort and a 100% adherence to protocol and retention rate in the distal radius cohort.

Conclusion: *A surge in hand edema after surgery was not detected in our cohorts. Hand edema detected by the water displacement method was found to be correlated with pain at multiple time points in the distal radius group. Our study protocol would indicate that a larger randomized controlled trial would be feasible. However, more investigations are needed to better understand hand and wrist swelling after surgery prior to proceeding.*

2.1 INTRODUCTION

Edema is defined as an excess of fluid in the extra- and intracellular spaces within the body,[13] and can be a common sequelae following surgical insult. Following hand and wrist surgery, this can manifest acutely as a change in skin tautness, hand colour and loss of defined anatomical landmarks. Prolonged edema, however, may have lasting effects on joint range of motion, scar formation, tissue mobility and esthetics of the hand. Edema has therefore been presumed to relate to post-surgical pain, function and patient outcomes. Evaluation of hand and wrist edema is thus a critical component of a clinician's and therapist's assessment. It can allow for a trajectory of a patient's recovery and offer valuable feedback for ongoing treatments.

Published literature on the objective evaluation of hand edema after surgery has mainly been limited to single time point evaluations or evaluations in the subacute phase. Husby et al explored the efficacy of non-steroidal anti-inflammatories on acute postoperative hand swelling in patients undergoing carpal tunnel release and limited fasciectomy for Dupuytren's contracture. The hand swelling assessment was completed 72 hours post operatively and compared to a single preoperative measurement.[138] Baker et al assessed the effect of hand elevation on early postoperative hand swelling in patients undergoing fasciectomy or trapeziectomy.[139] Hand volume measurements were taken on the day of surgery and 24 hours after surgery. Although these studies offer some insight on hand edema during the acute postoperative period, the translation is limited with only a single measurement during the immediate postoperative period. This limits the ability to provide conclusions about the evolution of hand edema throughout this critical phase. Other studies that have more longitudinal data on hand edema have generally only included patients weeks or months after the initial injury or surgery, without any measurements during the acute postoperative period.[140,141] To our knowledge, comprehensive reference data when assessing the normal longitudinal development of hand edema in the acute postoperative phase is limited. Moreover, the correlation of acute postoperative edema using objective data to postoperative pain, function and range is not well studied.

Despite this gap in objective reference values, therapy treatments are often instituted postoperatively in order to prevent or treat edema. Conventional edema therapy includes the combination of various methods that attempt to reduce, mobilize and clear postoperative hand and wrist swelling. Some of the methods include elevation, cryotherapy, external compression, manual edema mobilization, active and passive exercises and various types of massage. The current literature involves substantial heterogenicity of treatments, patients and outcomes preventing a synthesis for standard recommendations regarding edema management.[21] Nonetheless, a combination of the above therapies seem to be most commonly used amongst physicians and therapists.[21,50,136,142,143] Despite the best efforts and protocols, a subset of the postoperative population continues to have persistent hand and wrist swelling following surgery, resulting in undesired stiffness, pain and delays in return to function.

Tranexamic acid (TXA) is a lysine analog that acts as a competitive antagonist on plasminogen, an inactive substrate that once activated initiates clot breakdown (fibrinolysis). In effect, when TXA binds to plasminogen it prevents the activation of plasmin, essentially stabilizing existing clots and obstructing fibrinolysis. This has led to TXA's mainstream use as an antifibrinolytic and its use in surgical disciplines for decades to aid in reducing intraoperative blood loss and consequent transfusions.[54,84,103,110] However, additional evidence has shown that without active turnover to plasmin and resultant by-products, TXA may also reduce associated proinflammatory effects.[58] With the potential for both reduced surgical bleeding and inflammation, TXA has recently shown promising results in also curbing postoperative edema and ecchymosis in some surgical specialities. A systematic review and meta-analysis comprising 332 patients across five randomized clinical trials in the field of plastic surgery showed statistically significant reductions in facial edema and ecchymosis in three out of the five studies and an average decrease in blood loss of 41.6mL with the use of TXA compared to control groups.[130] These results are consistent in other surgical studies for nasal surgery and septorhinoplasty. Systematic reviews and meta-analyses in otorhinolaryngology surgery demonstrated that perioperative TXA

successfully reduced edema and ecchymosis for both nasal and rhinoplasty procedures.[133–135] These surgical studies support the potential for TXA outside of its traditional use. Specifically, when attempting to address the detrimental effects of postoperative hand and wrist edema, TXA provides an intriguing prophylactic inquiry.

The goal of this study was to evaluate the course of acute hand and wrist swelling after commonly performed hand and wrist procedures. We aimed to correlate acute hand edema with other reported outcome measures including postoperative pain, function and range of motion. Lastly, we examined the feasibility of a randomized controlled trial comparing the effects of tranexamic acid versus placebo on hand and wrist edema following hand and wrist surgery - a novel use of this medication.

2.2 METHODOLOGY

2.2.1 Study Design and Patients

This was a prospective, randomized, placebo-controlled, double-blinded study designed to test intravenous tranexamic acid's effect on swelling after Dupuytren's limited fasciectomy surgery or open reduction and internal fixation (ORIF) of distal radius fractures. These pathologies have a high incidence and rate of surgical intervention. Notably, they have also been associated with persistent swelling and stiffness postoperatively.[136,138,140,144] Following Health Canada and the Western University Research Ethics Board approval, the trial was registered at ClinicalTrials.gov (NCT04907812). An internal research grant from the University of Western Ontario was obtained. Informed consent was obtained from each study participant prior to proceeding and all rights were protected throughout their participation. From October 2021 to March 2022 all patients referred to the Hand and Upper Limb Clinic in London, Ontario, Canada were assessed for participation in the study. Patients ≥18 years old undergoing either a limited fasciectomy for Dupuytren's contracture or open reduction and internal fixation of a distal radius fracture using a volar approach were included. The exclusion criteria included use of an alternative or additional approach for distal radius fractures, revision surgery, known lymphedema or lymph node dissection of the operative arm, cardiovascular disease, cerebrovascular conditions, thromboembolic disorders, seizure disorder, renal failure, colour vision disturbances, currently pregnant or breastfeeding, current use of hormone contraceptive or known hypersensitivity to tranexamic acid.[67] Patients eligible for the study were provided a letter of information and consent. Once informed, those that wished to proceed provided consent and were assigned a study ID. The distal radius ORIF cohort and Dupuytren's limited fasciectomy were grouped independently. The Dupuytren's cohort were stratified for severity of disease to ensure parity between groups; patients with a MCP contracture ≤50°, a PIP contracture ≤40° were defined as mild and patients with a MCP contracture >50°, a PIP contracture >40° or more than 2 fingers involved were defined as severe. Each defined group were then randomly assigned to receive either intravenous (IV) tranexamic acid

or placebo (0.9% sodium chloride solution). The inpatient pharmacist completed the randomization using a computer-generated randomizer, using 1:1 randomization with blocks of 10 patients. Those enrolling patients into the study were not aware of the randomization process to maintain concealed allotment. The patient, surgeon and clinical staff involved in clinical evaluation or patient outcomes were also blinded to the drug preparation and solution administered.

2.2.2 Study Medication Dosing and Timing

A flow diagram of the interventions and measurements are presented in Figure 12. The dosing of TXA in the clinical setting remains largely empirical. This has been reflected in the breadth of IV dosing regimens reported ranging from a standard 1-gram intravenous dose to weight-based dosing. A systematic review of the effect of TXA on surgical blood loss demonstrated a drug total range of 5.5 to 300mg/L across 104 trials.[84] A subsequent meta-regression from this study suggested that the effect of TXA on blood loss did not vary over these dose ranges.[84] When using a fixed dose of TXA, Franz et al showed no difference in blood product administration in patients <100 kilograms (kg) versus those that were ≥100kg.[85,86] As TXA's effect on fibrinolysis is concentration dependent, multiple dose regimes have shown some promise in various studies.[94,95] Given this, for this study we chose to simplify our protocol to use a standard fixed dose of 1-gram of tranexamic acid given both twenty minutes before skin incision followed by a second dose two-six hours postoperatively.

The study medications were prepared by the inpatient pharmacist after randomization. The pharmacist prepared two doses of either 1% (10mg/mL) of tranexamic acid solution with a desired concentration of 1 gram in 100mL bag of 0.9% sodium chloride or a standard 100mL bag of 0.9% sodium chloride. The two bags of study drug or placebo were labelled in the same fashion, identical in size, quantity and colour (Figure 13). The prepared doses were delivered to the perioperative anaesthesia unit for administration. Both doses were administered by a physician on the study team. Both the physician and the patient were blinded to the medication given. The first dose was administered in the

preoperative regional anaesthesia area before entering the operative room within twenty minutes before skin incision. The second dose was administered between two to six hours after the first dose in the surgical day care unit. A Spectrum IQ Infusion System (Baxter) was used for intravenous drug administration at a rate of 5mL per minute (50mg/min) over a total of twenty minutes as per manufacturer's instruction.[67]

(a)

| Screened | Screened prior to eligibility assessment (n=21) |

↓

| Enrollment | Assessed for eligibility (n=21) |

→

Excluded (n=6)
♦ Thromboembolic history (3)
♦ Refused to participate (3)

↓

Randomized (n=15)

Allocation

Allocated to Tranexamic Acid (n=8)
♦ Received Tranexamic Acid (n=8)

Allocated to placebo (n=7)
♦ Received placebo (n=7)

Follow-Up

Lost to follow-up (n=0)

Lost to follow-up (n=3)
♦ COVID restrictions (2)
♦ Relocation (1)

Assessment

Assessed hand volume (n=8)

Assessed range of motion (n=8)

Assessed reported outcomes (n=8)

Assessed feasibility outcomes (n=8)

Assessed hand volume (n=4)

Assessed for range of motion (n=4)

Assessed for reported outcomes (n=7)

Assessed for feasibility outcomes (n=7)

(b)

Figure 12: Study flowchart for the (a) Dupuytren's, and (b) distal radius cohorts
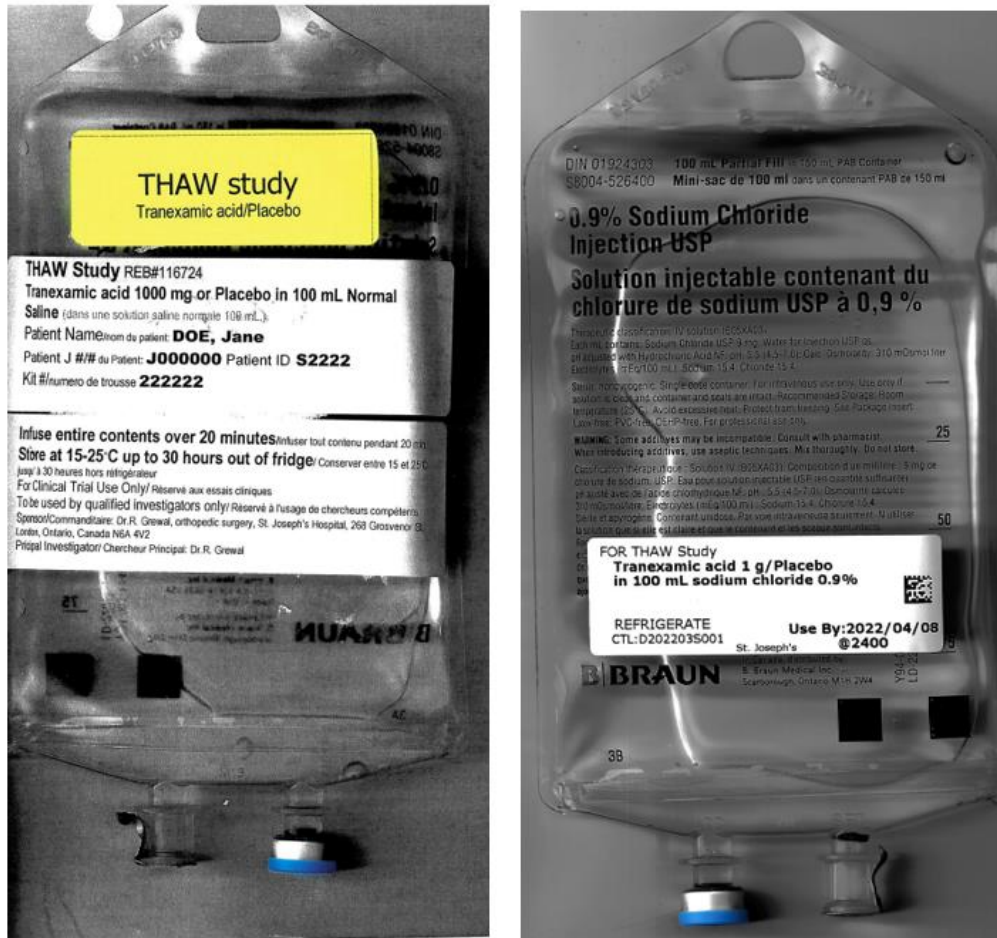
Figure 13: Two doses of 100mL intravenous bags with either 1% (10mg/mL) of tranexamic acid solution with a desired concentration of 1 gram in 100mL bag of 0.9% sodium chloride or a standard 100mL bag of 0.9% sodium chloride were prepared for each patient

2.2.3 Surgical Technique and Postoperative Care

All enrolled patients received their surgery by a fellowship trained hand and wrist surgeon under regional anaesthesia with sedation. All patients received prophylactic IV antibiotics prior to skin incision. A non-sterile tourniquet was inflated throughout the case and meticulous hemostasis was achieved prior to wound closure.

In the Dupuytren's cohort, a Bruner style incision was used to gain access to the diseased area. The neurovascular bundles were identified and protected prior to isolation and transection of the Dupuytren's cords. If there was inadequate correction

with resection alone, a joint capsular release was completed as per the surgeon's discretion. Patients were placed in an extension splint prior to departing the operating room. Patients followed up at one week, two weeks, six weeks and three months. On the first follow up, the operative splint was removed, a customized thermoplastic splint was fashioned by the occupational therapist and a standard active hand therapy protocol was commenced. This included active and passive stretching, external compression, edema mobilization message and whirlpool therapy. The therapy was completed at a single centre but was tailored to the individual patient. The patients were instructed to wear this extension-based splint at nighttime for the first three months following surgery. Sutures were removed at the two-week followed up.

In the distal radius cohort, a modified Henry approach was used to gain access to the distal radius. Once a satisfactory reduction was obtained, a volar locking plate (Synthes) was used to maintain reduction and a standard volar splint was applied. The patients followed up at two weeks, three-four weeks, six weeks and three months. On the first follow up the postoperative splint was removed, and subsequent immobilization was at the discretion of the treating surgeon. The majority chose to transition to a removable splint but, if indicated or based on surgeon preference, patients were immobilized for an additional two to four weeks. If converted to a splint, the patient was instructed to wear it regularly until the six-week follow up. If radiographic union was confirmed, a progressive wean of the splint was instituted. In the event of continued rigid immobilization, a fiberglass cast was placed for an additional two to four weeks; however, hand therapy for digit range of motion was instituted. Otherwise, hand therapy was commenced in a similar fashion to the Dupuytren's cohort.

2.2.4 Outcomes

Patient demographic and preoperative characteristics including age, sex, hand dominance, smoking status were collected for comparison between treatment groups. The primary outcome measure for this study was the evaluation of the change in hand volume over time. At each follow up all patients underwent objective hand volume evaluation using both water displacement and Figure-of-Eight methods. All patients

underwent hand volume measurements of both the operative and nonoperative hand preoperatively and at each subsequent follow up. For the water displacement method, a volumetric measuring device (Jamar Health Products Inc, Greendale, WI) was used for all measurements. This volumetric device is reliable and accurate to within 1% of the total volume.[24] To begin the assessment, the volumeter was filled with tepid water until it began to overflow into a collection beaker. The collection beaker was then emptied to zero the device. The patient was instructed to stand and remove all jewelry. The hand was positioned with the thumb toward the outflow spout, fingers adducted, forearm pronated and perpendicular to the bottom of the device. The patient then lowered their hand slowly until the webspace between the third and fourth finger was resting on a dowel inside the volumeter. The dowel was used to ensure consistent depth was obtained for all individual and contralateral measurements. Once the overflow had stopped completely, the collected water was placed in a graduated cylinder and a measurement in milliliters (mL) was obtained. Measurements of the contralateral hand were also obtained at each follow up interval. All surgical wounds were directly submerged into the water at the discretion of the surgical team. If a wound was deemed dehisced or infected, a Tegaderm® dressing was placed on both the operative and nonoperative hand to allow for comparative evaluation.

The Figure-of-Eight method was also used to objectively measure hand edema. Patient's nonoperative and operative hands were measured preoperatively and at the stated follow ups. A standard 1.2 cm wide, retractable tape measure was used. The patient was seated with the forearm supported and placed in a supinated position. They were instructed to maintain a neutral position of the wrist in flexion/extension and radial/ulnar deviation. The tape measure was then passed with uniform tension along the defined anatomical landmarks as illustrated in Figure 14, as described by Leard et al.[29] The total volume was measured in centimeters.
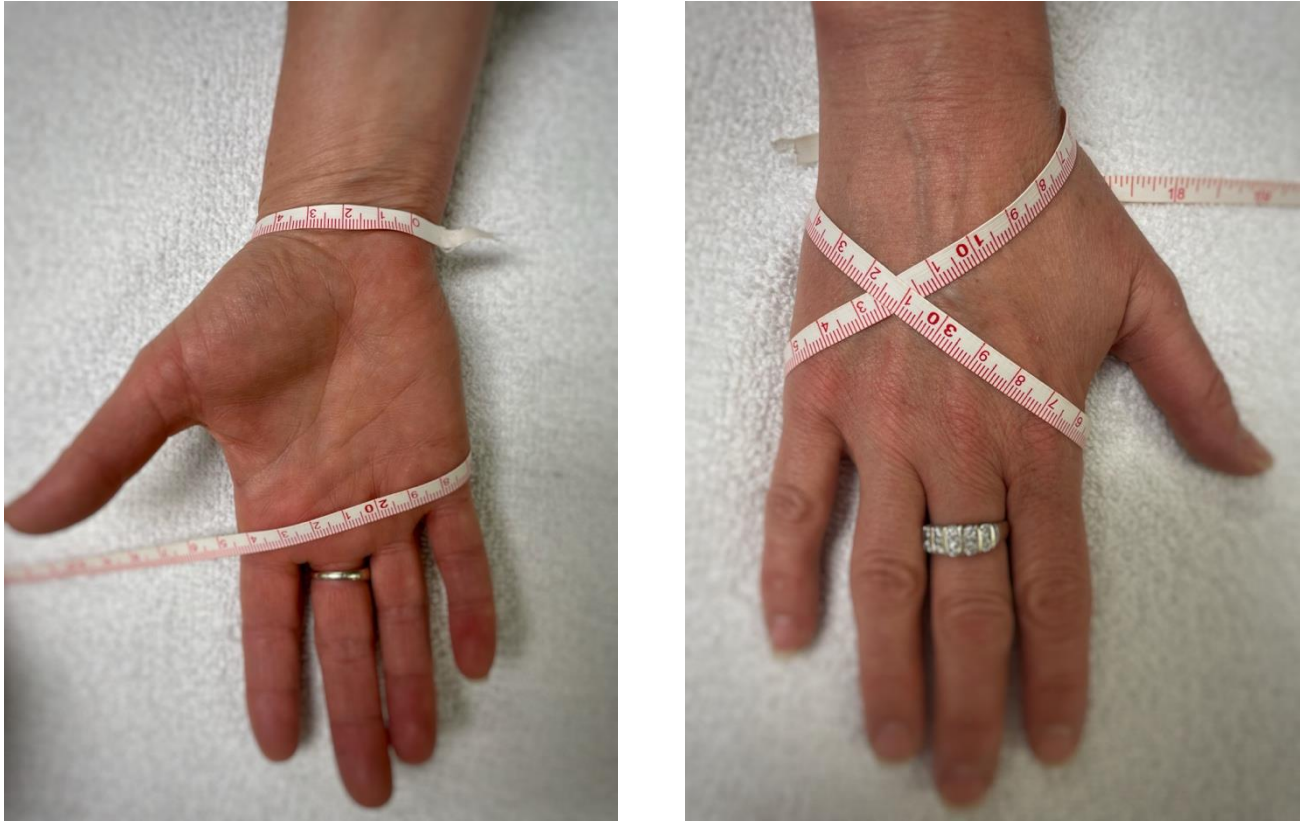
Figure 14: Figure-of-Eight method: (1) ulnar styloid, (2) crossed volarly to the radial styloid, (3) crossed dorsally and diagonally over the dorsal fifth MCP joint, (4) crossing volarly and transversely over the volar second MCP joint, (5) crossing dorsally and diagonally back to the starting point

Secondary outcomes include patient rated hand and wrist evaluation (PRWHE), Numeric Rating Scale (NRS) for postoperative pain, tip-to-palmer crease distance measurements and feasibility outcomes. The PRWHE is an anatomic region-specific, patient reported outcome measuring tool that is used to assess a patient's pain and function. The total score is out of one-hundred with equal weight for pain and function; a higher score would indicate higher levels of pain and/or decreased function. Changes in a score less than nine points are considered measurement error, and changes of seventeen or twenty-four are considered the minimal clinically important difference when comparing groups or an individual, respectively. The NRS is a patient reported outcome tool that evaluates pain on a scale from 0-10. A reduction of two points has been found to be clinically significant. The average tip-to-palmer crease was obtained for the operative finger(s) for the Dupuytren's group and for all fingers in the distal

radius group using the landmark-to-landmark method. The junction between the distal nail fold and nail was used distally and the line joining the distal palmar crease ulnarly with the proximal palmar crease radially was the proximal landmark. The results were obtained in centimeters.

All outcome measurements were collected preoperatively and at each subsequent follow up, with the exception of the NRS which was evaluated for the first seven days postoperatively. All outcome measures were recorded and stored in a secure database by the research team.

2.2.5 Statistical analysis

A formal sample size calculation was not undertaken for this feasibility study. Using the rule of thumb rationale for pilot studies by Julious, we chose a goal of recruitment of twelve patients per cohort.[145] This is consistent with other sample sizes described in pilot and feasibility studies, as well as hand edema RCTs.[136,146] Statistical analysis was performed using the Statistical Package for Social Sciences (Version 20; Chicago, Illinois). For volume analysis, both hands were measured preoperatively and at four postoperative follow ups. For the Dupuytren's cohort, the preoperative measurement of the operative hand was used as the control for each patient and subsequent measurements were analyzed and compared to this control. This was analyzed as both volume change (mL) and percent change. For the distal radius cohort, both the preoperative ratio and difference of water displacement of the injured hand were compared to the non-injured hand at each time point. The preoperative values were used to compare to each subsequent follow up to produce a value reflective of total change in hand volume. Based on the work by Waylett-Rendall et al, a difference of 10mL with a normal hand and 12mL in an edematous hand is considered indicative of clinically significant change in tissue volume.[24] For the Figure-of-Eight method, a volume change of more than 0.56cm has been considered indicative of true change in hand size.[29] The NRS was collected at the first follow up. The remaining assessments yielded data points at all follow ups.

Feasibility objectives were established prior to the outset and analyzed to assess viability for a larger clinical trial. The objectives for this aspect were determined *a priori* based on previous feasibility guides and estimations based on clinical experience:[147–153] five patients per month recruitment, 90% of all recruited patients perform hand volume measurements at all designated time intervals, 90% of all patients receive scheduled dose of TXA preoperatively twenty minutes before skin incision and two to six hours postoperatively and 80% retention rate.

Each pathology was initially analyzed as a large cohort to assess for trends related to postoperative hand edema and correlations between the secondary outcomes. The data were then unblinded and analyzed to assess for preliminary tendencies and effects of TXA in relation to the primary and secondary outcomes. We used descriptive statistics for demographic data and sample characteristics. Wilks-Shapiro normality testing was used to test for normally distributed data, and *t-tests* were used to identify differences between variables. Pearson correlation tests were used to assess for relationships amongst tested variables.

2.3 RESULTS

2.3.1 Limited Fasciectomy

Twenty-one consecutive patients with Dupuytren's disease were assessed for study eligibility. Fifteen patients met study eligibility and were enrolled. Patient demographics for each cohort are summarized in Table 1. The exclusions in the Dupuytren's group included three patients with medical conditions (previous thromboembolic events) and three patients that refused participation. Three patients in the Dupuytren's cohort did not complete the entire protocol due to in-person follow up restrictions from the COVID-19 pandemic. The PRWHE data was still collected until study conclusion for these three patients. However, a total of thirteen and twelve patients were included in the clinical measurements at the six week and three months follow up, respectively. The completed swelling data and patient reported outcome data from these patients were included in the analysis. No patient required a joint capsular release or skin graft. The summary of the results for the limited fasciectomy cohort are summarized in Table 2.

Table 1: Demographics	Dupuytren's (n=15)	Distal Radius (n=8)
Age	61.8 (36-76)	54.9 (26-71)
Gender	Female – 7 Male - 8	Female – 5 Male - 3
Smoker	No - 14 Yes - 1	No – 8 Yes - 0
Dominant Hand	Dominant – 5 Non-dominant - 10	Dominant – 1 Non-dominant - 7
Surgical Time	0:56 (0:18-1:29)	1:19 (0:29-2:22)
Tourniquet Time	0:36 (0:09-1:03)	1:13 (0:27-2:00)

Table 1: Patient demographics: Age, surgical time and tourniquet time are presented as mean and range (min-max).

A mean percent volume change (as measured by water displacement relative to preoperative values) was demonstrated at postoperative week 1, week 2, week 6 and week 12. The values were 1.4% (SE, 1.1, p=0.23), 1.37% (SE, 0.9, p=0.14), 0.47% (SE, 1.3, p=0.72) and -1.2% (SE, 1.4, p=0.40), respectively. The absolute mean volume change from preoperative values of the operative hand at postoperative week 1, week 2, week 6 and week 12 was 8.8mL (SE, 6.0), 7.3mL (SE, 4.3), 1.3mL (SE, 5.8) and -7.3 (SE, 6.3), respectively (Figure 15).

Figure-of-Eight measurements demonstrated a mean change (in centimeters) from preoperative values of the operative hand at postoperative weeks 1, 2, 6 and 12 of 0.91 (SE, 0.28, p=0.006), 0.77 (SE, 0.35, p=0.048), 0.67 (SE, 0.38, p=0.10), 0.30 (SE, 0.31, p=0.35), respectively.

The mean NRS score recorded in the first week postoperatively was 2.10 (SE, 0.46). The mean baseline PRWHE score was 19.2 (SE, 6.3). When separating pain and functional scores from the PRWHE, the mean baseline scores were 10.0 (SE, 3.6) and 9.2 (SE, 3.3), respectively. Mean postoperative total PRWHE scores at postoperative weeks 1, 2, 6 and 12 were 50.0 (SE, 5.8), 37.9 (SE, 5.4), 16.3 (SE, 3.4) and 7.07 (SE, 1.7), respectively. Mean postoperative pain scores were 15.73 (SE, 3.2) at week 1, 16.1 (SE, 2.3) at week 2, 11.3 (SE, 2.0) at week 6 and 5.6 (SE, 1.4) at week 12. Mean postoperative function score were 34.2 (SE, 4.0) at week 1, 21.9 (SE, 3.5) at week 2, 4.9 (SE, 1.5) at week 6 and 1.9 (SE, 0.6) at week 12 (Figure 16).

The difference of postoperative PRWHE means compared to the preoperative baseline values were statistically significant at week 1 (p<0.001) and week 2 (p=0.002), while the differences at week 6 (p=0.49) and week 12 (p=0.08) were not. With the isolated pain and functional scores from the PRWHE, the differences in the mean of the preoperative pain scores were not statistically significant at any postoperative time point. The difference in the mean preoperative function score and postoperative function score at

week 1 (p<0.001) and week 2 (p=0.001) were statistically significant but were not significant at week 6 (p=0.096) and week 12 (p=0.051).

The average preoperative tip to palmar crease of the operative finger(s) measured in centimeters was 0.4 cm (SE, 0.2). The average postoperative tip to palmar crease was 6.0 cm (SE, 0.5, p<0.001), 4.1 cm (SE, 0.4, p<0.001), 2.2 cm (SE, 0.4, p=0.001) and 2.5 cm (SE, 0.4, p=0.003) on week 1, 2, 6 and 12, respectively.

Pearson correlation showed a positive correlation between week 1 measurements of water displacement and PRWHE (r=0.55, p=0.034). Week 6 measurements showed a positive correlation between water displacement and average tip to palm measurements (r=0.57, p=0.042). Remaining Pearson correlations of the follow up time points did not demonstrate statistically significant relationships.

There were two patients that experienced superficial wound infections. Both infections resolved after one week of oral antibiotic therapy. One other patient also incurred a residual flexion contracture of the proximal interphalangeal joint acutely after surgery requiring enhanced hand therapy and splinting. They did not recover full extension by the final follow up in this study. No patient required a volar capsular release in this cohort.
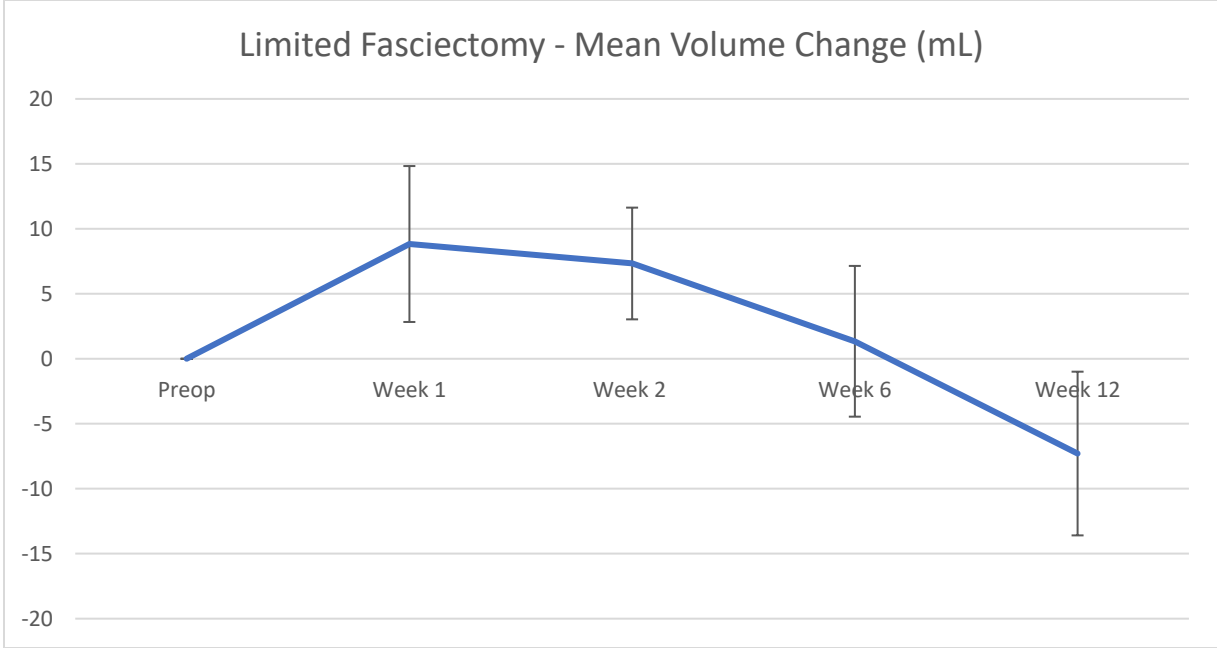
Figure 15: Summary of mean hand volume changes after limited fasciectomy.

(A)
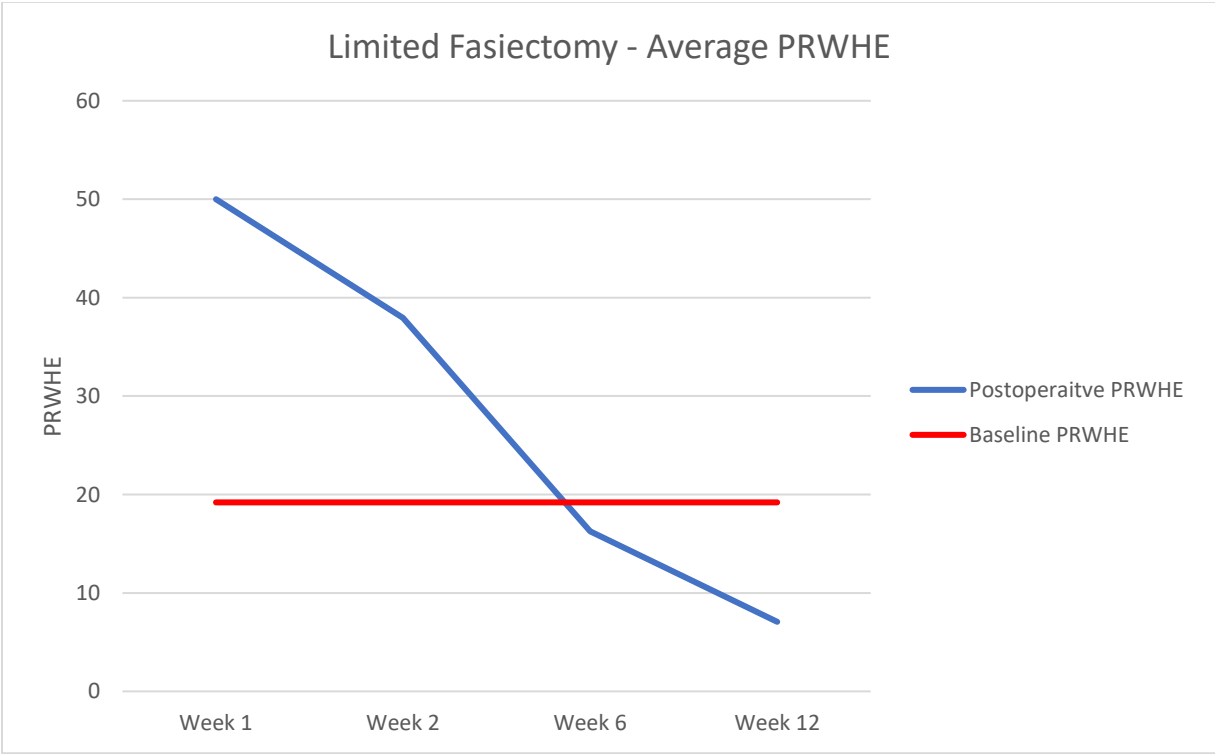
(B)
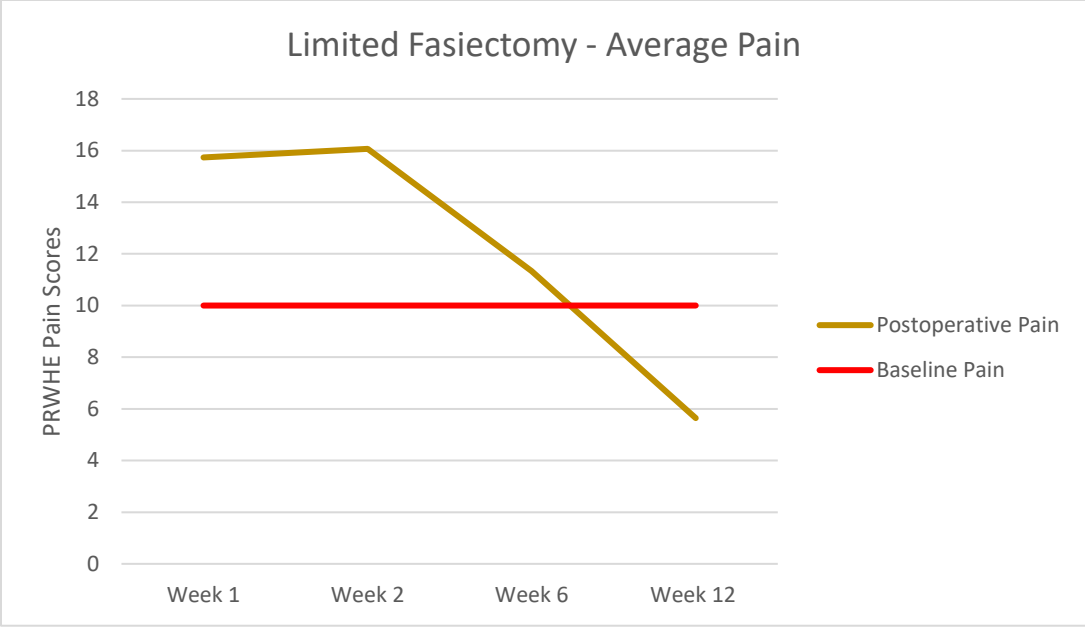
(C)
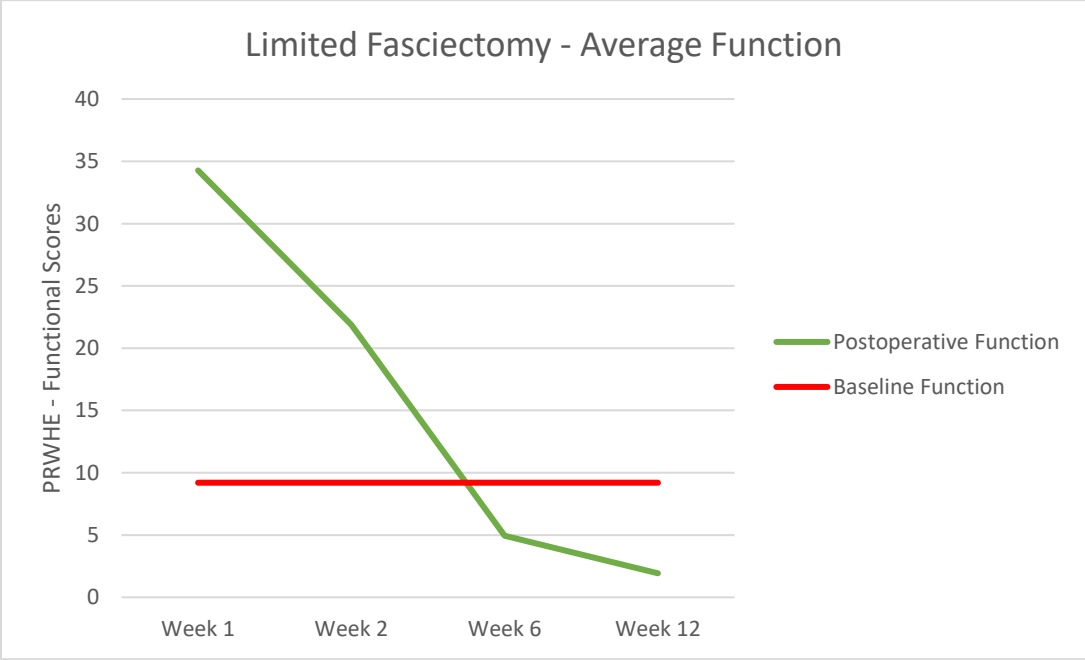
Figure 16: Average (A) PRWHE Score, (B) Pain scores, (C) Functional scores of patients undergoing limited fasciectomy

Table 2: Limited Fasciectomy Results Summary					
	Preoperative	**Week 1**	**Week 2**	**Week 6**	**Week 12**
Water displacement (% of unaffected side)		1.4% + 1.1	1.37% + 0.9	0.47% + 1.3	-1.2% + 1.4
P value		0.23	0.14	0.72	0.40
Figure-of-Eight (cm)		0.91+ 0.28	0.77 + 0.35	0.67 + 0.38	0.30 + 0.31
P value		0.006	0.048	0.10	0.35
NRS		2.10 + 0.46			
PRWHE	19.2 + 6.3	50.0 + 5.8	37.9 + 5.4	16.3 + 3.4	7.1 + 1.7
P value		<0.001	0.002	0.49	0.08
Pain (from PRWHE)	10.0 + 3.6	15.73 + 3.2	16.1 + 2.3	11.3 + 2.0	5.6 + 1.4
P value		0.10	0.09	0.63	0.56
Function (from PRWHE)	9.2 + 3.3	34.2 + 4.0	21.9 + 3.5	4.9 + 1.5	1.9 + 0.6
P value		<0.001	0.001	0.10	0.05
Tip to Palmar Crease (cm)	0.4 + 0.2	6.0 + 0.5	4.1 + 0.4	2.2 + 0.4	2.5 + 0.4
P value		<0.001	<0.001	0.001	0.003

2.3.2 Distal Radius

Twenty-three consecutive patients with distal radius fractures were assessed for study eligibility. Eight patients met study eligibility and were enrolled (Table 1). Seven patients were excluded for medical reasons (three with previous thromboembolic events, two with seizure disorders, one with a lymph node dissection of the operative arm, one with COVID-19 that prohibited operative care), six declined to participate (four for follow up concerns, two for medication concerns), two were excluded for dual approaches. All patients from this cohort that were included in this study completed the study protocol. All patients began active motion protocol with splint application at the two weeks follow up; no patient required additional cast therapy after the first follow up. The summary of results for this cohort are reported in Table 3.

The mean percent ratio of the operative hand compared to the nonoperative hand using water displacement preoperatively was 15.5% (SE, 2.3). At the 2 weeks follow up the mean percent ratio was 9.0% (SE, 0.9, p=0.02), at 3 weeks it was 9.6% (SE, 1.6, p=0.06), at 6 weeks it was 6.5% (SE, 2.1, p=0.02) and at 12 weeks it was 3.9% (SE, 1.9, p=0.01). The difference in mean preoperative hand volume percentages compared to postoperative values were statistically significant for week 2, week 6 and week 12. The mean difference in volume of the operative hand compared to the nonoperative hand was 68.1mL preoperatively (SE, 10.3), 39.6mL (SE, 4.8, p=0.014) at week 2, 42.2 (SE, 7.1, p=0.049) at week 3/4, 26.3 (SE, 6.4, p=0.01) at week 6 and 15.7 (SE, 6.7, p=0.005) at week 12 (Figure 17). The average change in water displacement at the follow up measurements compared to the preoperative values were statistically significant at all time points.

Figure-of-Eight measurements demonstrated a mean change (in centimeters) from preoperative values of the operative hand at postoperative week 1, week 2, week 6 and week 12 of -0.89 (SE 0.65, p=0.13), -1.39 (SE 0.40, p=0.044), -1.08 (SE 0.30, p=0.13), -1.74 (SE 0.41, p=0.06), respectively.

The mean NRS score recorded in the first week postoperatively was 4.29 (SE, 0.79). The mean baseline PRWHE score was 84.9 (SE, 3.3). Mean postoperative total PRWHE scores at postoperative week 2, week 3-4, week 6 and 12 were 72.6 (SE, 4.7, p=0.02), 62.2 (SE, 4.6, p=0.01), 51.6 (SE, 4.5, p<0.001) and 19.4 (SE, 6.4, p<0.001). The difference of the mean postoperative PRWHE compared to the preoperative values were statistically significant at all time points.

When separating pain and function from the PRWHE, the mean baseline scores were 35.8 (SE, 3.3) and 49.2 (SE, 0.7), respectively. Mean postoperative pain scores were 25.5 (SE, 3.8) at week 2, 20.6 (SE, 2.6) at week 3-4, 22.3 (SE, 3.6) at week 6 and 11.6 (SE, 4.1) at week 12. Mean postoperative function score were 47.1 (SE, 1.4) at week 2, 41.6 (SE, 3.3) at week 3-4, 29.3 (SE, 2.2) at week 6 and 7.8 (SE, 2.5) at week 12 (Figure 18). The differences in the mean preoperative pain scores were statistically significant at all postoperative time points. For mean postoperative function scores, there was only statistically significant difference at week 6 (p<0.001) and week 12 (p<0.001).

The average preoperative tip to palmar crease of the operative finger(s) measured in centimeters was 5.6 cm (SE, 0.5). Compared to preoperatively, the average postoperative tip to palmar crease was 4.2 cm (SE, 0.7, p=0.11), 2.7 cm (SE, 0.4, p=0.004), 1.4 cm (SE, 0.4, p<0.001) and 0.6 cm (SE, 0.4, p<0.001) on week 1, 3-4, 6 and 12, respectively.

Pearson correlation showed a strong, positive correlation between measurements of water displacement and PRWHE at preoperative (r=0.85, p=0.007), week 2 (r=0.77, p=0.03) and week 6 (r=0.574, p=0.14). More specifically, the Pearson correlation showed a correlation between water displacement and pain scores from the PRWHE at these time points. However, there was no correlation between volume measurements and the average NRS scores or PRWHE functional scores. The remaining Pearson correlations at residual follow up time points did not demonstrate statistically significant relationships.

There were no wound infections in the distal radius group. One patient developed signs of complex regional pain syndrome at the two-week follow up. The symptoms improved with the treatment with neuropathic pain medication and high-dose vitamin C. There were no complications associated with acute fixation failure, delayed union or loss of reduction.
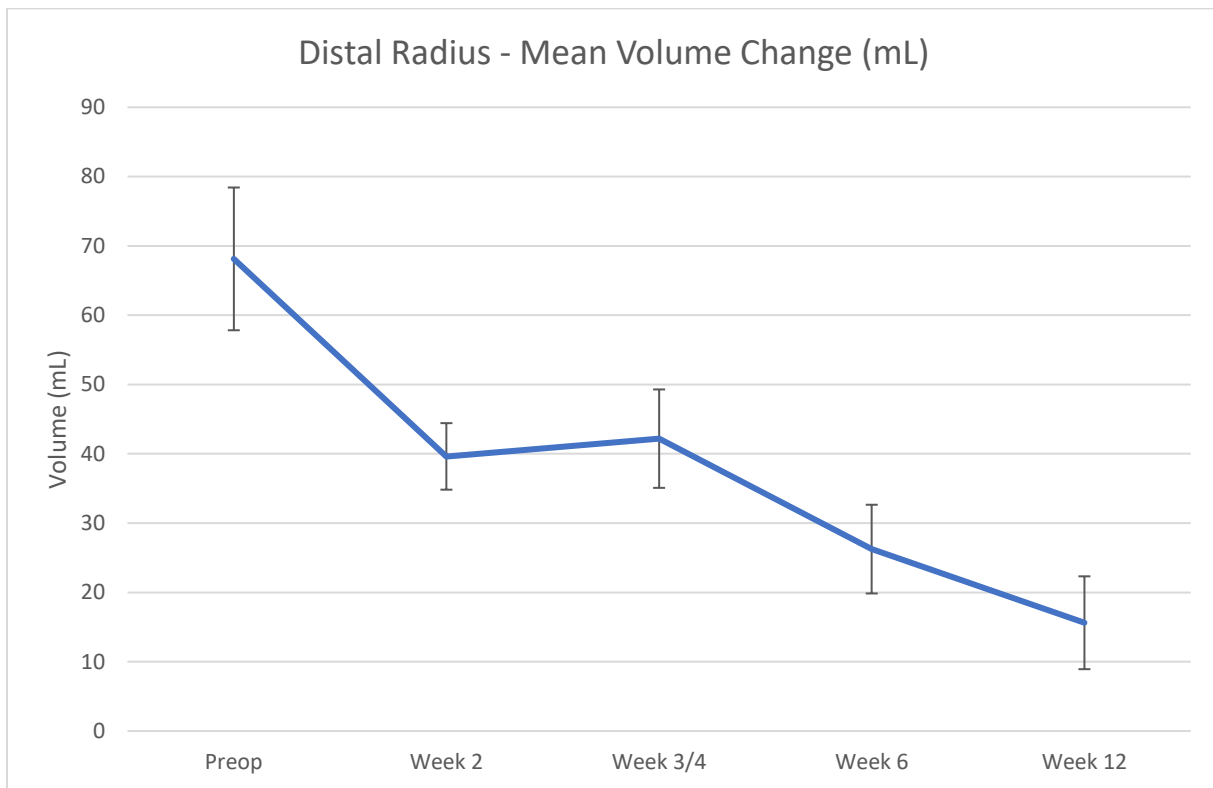
Figure 17: Summary of mean hand volume changes after distal radius ORIF

A)

Distal Radius - Average PRWHE

B)
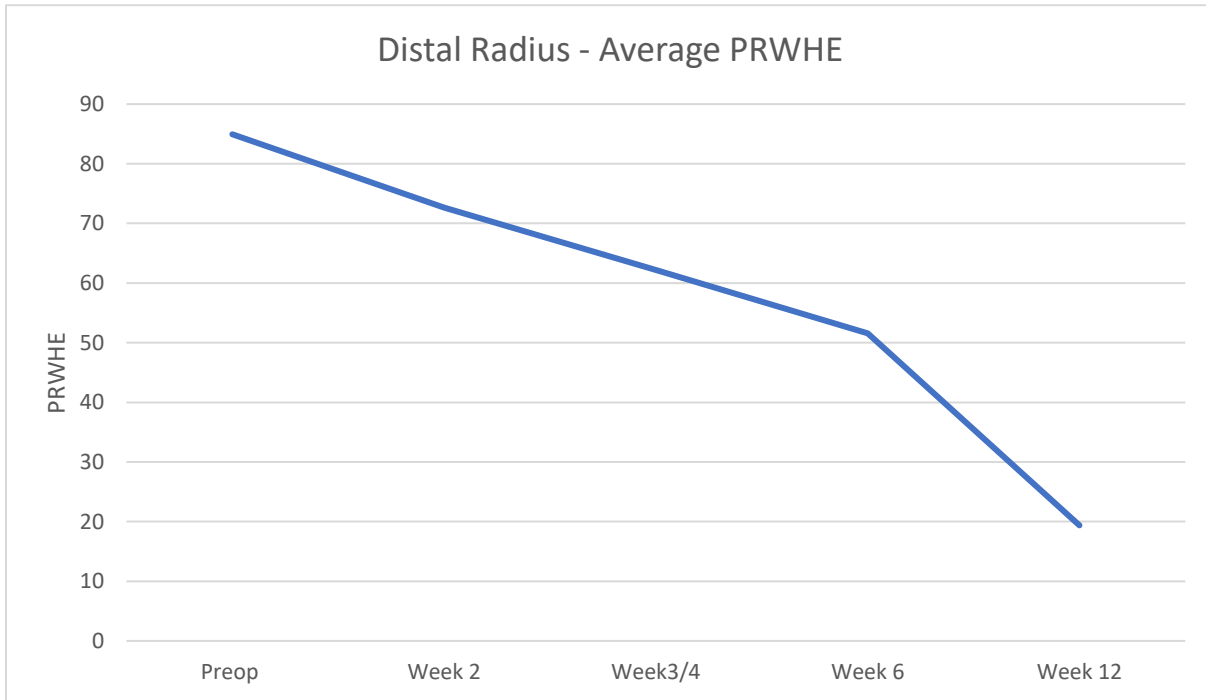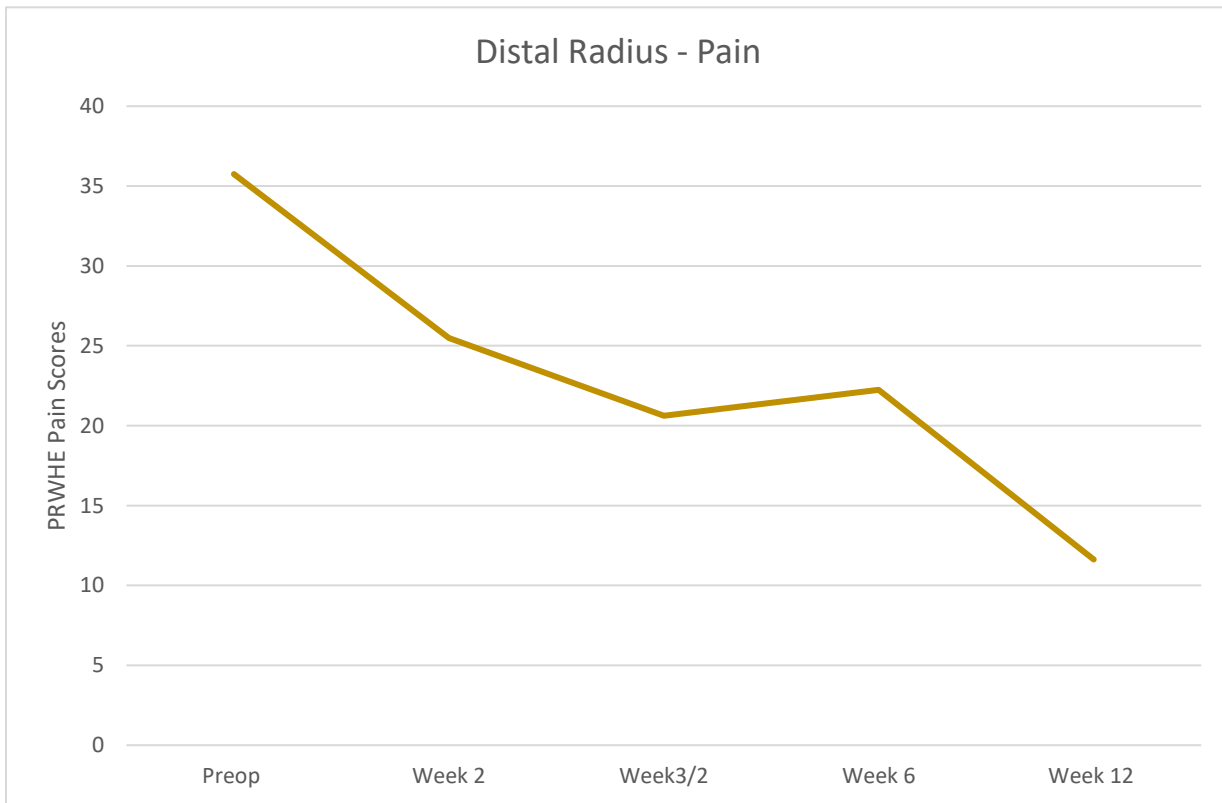
Distal Radius - Pain

C)
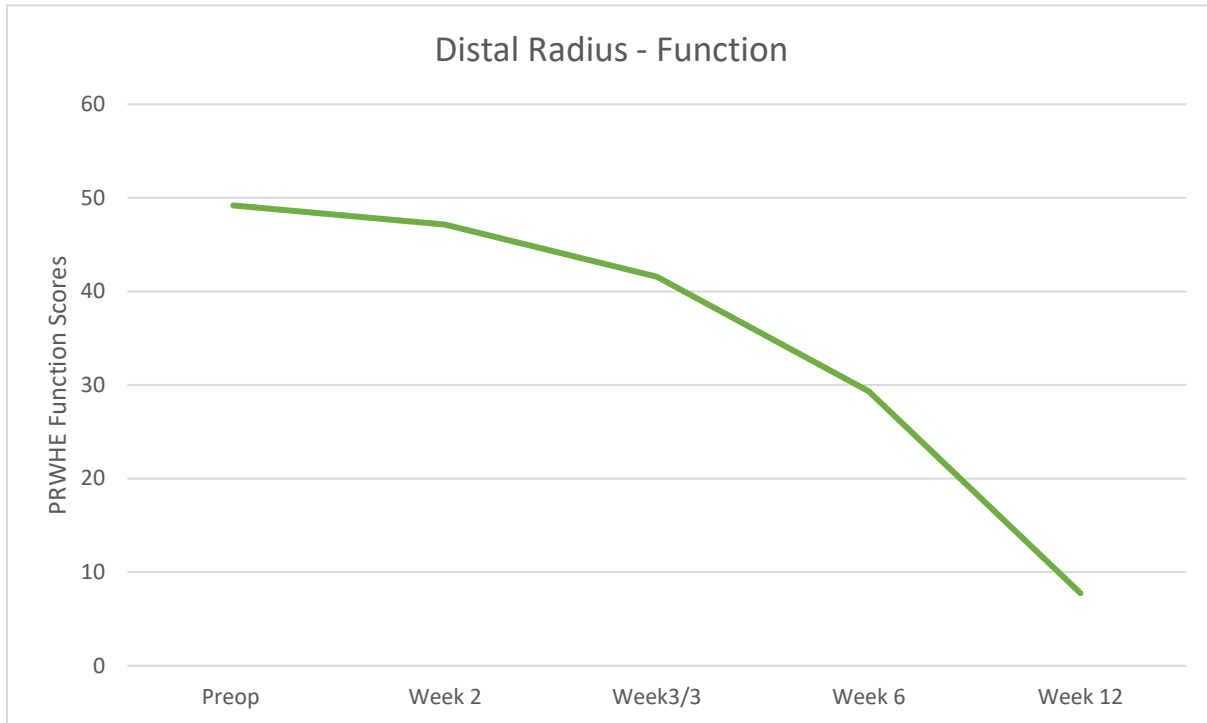
Figure 18: Average (A) PRWHE Score, (B) Pain scores, (C) Functional scores of patients undergoing distal radius ORIF

Table 3: Distal Radius Results Summary					
	Preoperative	**Week 2**	**Week 3/4**	**Week 6**	**Week 12**
Water displacement (% of unaffected side)	15.5 % + 2.3	9.0 % + 0.9	9.6% + 1.6	6.5% + 2.1	3.9% + 1.9
P value		0.02	0.06	0.02	0.01
Figure-of-Eight (mean change from unaffected side, cm)		-0.89 + 0.7	-1.39 + 0.4	-1.08 + 0.3	1.74 + 0.4
P value		0.13	0.04	0.13	0.06
NRS		4.29 + 0.8			
PRWHE	84.9 + 3.3	72.6 + 4.7	62.2 + 4.6	51.6 + 4.5	19.4 + 6.4
P value		0.02	0.01	<0.001	<0.001
Pain (from PRWHE)	35.8 + 3.3	25.5 + 3.8	20.6 + 2.6	22.3 + 3.6	11.6 + 4.1
P value		0.01	0.006	0.002	<0.001
Function (from PRWHE)	49.2 + 0.7	47.1 + 1.4	41.6 + 3.3	29.3 + 2.2	7.8 + 2.5
P value		0.19	0.06	<0.001	<0.001
Tip to Palmar Crease (cm)	5.4 + 0.5	4.2 + 0.7	2.7 + 0.7	1.4 + 0.4	0.6 + 0.3
P value		0.11	0.004	<0.001	<0.001

2.3.3 Measures of Feasibility

2.3.3.1 Recruitment

Active recruitment numbers of this trial between the months of October-January are displayed in Table 4. An average of five patients in the Dupuytren's group and three patients in the distal radius group were recruited per month. There was a 29% rate of exclusion in the Dupuytren's group and a 65% rate of exclusion in the distal radius group. Reasons for exclusion were heterogenic, but mainly included medical exclusions related to the drug label or refusal to participate.

2.3.3.2 Drug Administration

Assessing the application of the protocol, the average preoperative TXA dose for the Dupuytren's and distal radius groups were given fifty-seven and thirty-six minutes before skin incision, respectively. The average postoperative TXA dose for the Dupuytren's and distal radius groups were given two hours and twenty-four minutes and two hours and sixteen minutes after the first dose, respectively. As the preoperative dose was given in the preoperative anaesthesia block room by a member of the surgical team, the timing to skin incision under this protocol was unreliable. It was subject to operative room and block room delays. As such, only seven percent of patients in the Dupuytren's group and none of the distal radius cohort were given their preoperative dose within the desired twenty minutes prior to skin incision. However, sixty percent of the Dupuytren's group and one hundred percent of the distal radius group had their preoperative dose within one hour of skin incision. One patient in the Dupuytren's group received their postoperative tranexamic acid dose prior to two hours. Otherwise, all remaining patients in the Dupuytren's group and all of the distal radius group had their postoperative medication administered according to the established protocol of two to six hours after the first dose.

2.3.3.3 Collection of Outcomes

On average, each follow up assessment added ten to fifteen minutes to the patient's clinical visit. Our protocol included one extra follow up for the distal radius group that fell outside of our centre's typical follow up regimen. There was an eighty-seven percent and one-hundred percent response rate to the postoperative NRS survey. All patients in both cohorts completed the postoperative PRWHE scores at all follow ups. Eighty percent of patients in the Dupuytren's group completed all measurement outcome data including volume and range of motion measurements. This resulted in a twenty percent dropout rate in this cohort. Two of the three patients that did not complete the protocol deferred follow up appointments due to the ongoing COVID-19 pandemic. The other had relocated during the postoperative period. All patients in the distal radius cohort completed all aspects of the protocol, with a dropout rate of zero percent.

2.3.3.4 Patient and Examiner Feedback

Patient feedback was favourable for all methods to obtain the outcome measures. Two patients in the distal radius group experienced discomfort during their preoperative water displacement measurement. Two patients in the Dupuytren's cohort experienced discomfort during the water displacement testing at the first follow up. At the end of the protocol, most patients stated they would have participated again if given the opportunity. Examiner feedback demonstrated favourable support for completing both the drug and outcome measurement aspects of this protocol. A dedicated study team member independent of the operative or clinical team may be helpful in mitigating the common complaints of time constraints for some of these outcome measurements.

Table 4: Feasibility Outcomes		
	Distal Radius	**Dupuytren's**
Recruitment numbers per month (Oct-Jan)	Oct – 1 Nov – 3 Dec – 4	Oct - 10 Nov – 4 Dec – 1
TXA #1 - 1st dose to skin incision (mins)	Mean: 0:36 Median: 0:32	Mean: 0:57 Median: 0:52
TXA #2 – 1st dose to 2nd dose (hours)	Mean: 2:24 Median: 2:15	Mean: 2:16 Median: 2:09
NRS Response rate	6/8 (85.7%)	13/15 (86.7%)
Retention Rate	8/8 (100%)	12/15 (80%) 3/15 (20%) did not complete the protocol • 2 completed up to 3 weeks (COVID related) • 1 completed up to 6 weeks (away for winter)
Measurements	Water Displacement: 100% Figure of Eight: 100% Tip to Palm: 100% PRWHE: 100%	Water Displacement: 80% Figure of Eight: 80% Tip to Palm: 80% PRWHE: 100%

Table 4: Feasibility Results

2.4 DISCUSSION

Hand edema following surgical insult is a common sequelae. Although acute hand edema can often be successfully treated by a variety of conventional methods, some patients still experience persistent hand and wrist edema. This can be a devastating side effect with the added by-products of pain, stiffness and delays to work or normal activities. Despite strong anecdotal support, the evidence regarding acute hand edema and its relationship with these consequences is limited.

Our study was able to further the understanding of acute hand and wrist edema following surgery by collecting and evaluating prospective, short term, longitudinal data on patients undergoing limited fasciectomy for Dupuytren's disease and open reduction and internal fixation for distal radius fractures. In the Dupuytren's cohort, we did not find a statistically significant change in hand volume at any postoperative time point using water displacement. The Figure-of-Eight method did find a statistically significant difference at the initial postoperative follow up; however, the average difference was less than one centimeter. These results coincide with other studies that have investigated hand edema following limited fasciectomy. Baker et al measured hand edema with water displacement in patients preoperatively and 24 hours after undergoing limited fasciectomy.[139] This study randomized patients undergoing limited fasciectomy to receive either an elevation study protocol or the standard of care. In both study groups, the mean postoperative water displacement measurements compared to the preoperative value were below 10 mL. Although this study did show a change in edema after limited fasciectomy, the overall change in acute hand edema following surgery did not reach clinical significance. Notably, the lack of significant change in hand volume in this study may also be related to deficiencies in measurement selection. Although water displacement and figure of eight methods are the gold standard in recording whole hand edema, limited fasciectomy procedures are generally confined to the fingers and palm. At the onset of this study it was thought that limited fasciectomy would result in global hand edema and therefore be appropriately captured with the chosen measurement tools in this study. However, this was not reflected in our volume measurements. There was, however, visually apparent edema that was often isolated to

the operative finger(s). A more specific measurement of finger edema such as the ring gauge or finger circumference may have provided a more sensitive measurement of edema in this cohort. Interestingly, by measuring whole hand edema we did encounter less volume in the operative hand at the three months follow up using water displacement. This finding may relate to the small sample size but may also demonstrate a degree of atrophy of the intrinsic hand muscles that relates to disuse during the early postoperative phase. Additionally, although patients in the Dupuytren's group experienced an improvement of the PRWHE and its individual components, these improvements did not reach statistical or clinical significance.

Perhaps most notably, the Dupuytren's cohort experienced a statistically significant increase in tip to palmar crease distance at all follow ups postoperatively. It is important to highlight that preoperatively, patients with Dupuytren's disease generally have flexion contractures (difficulty with digit extension); however, the patient's ability to flex the digit is usually unaffected. Although the goal of limited fasciectomy is to improve the flexion contracture of the finger, postoperative stiffness of the finger can lead to a residual flexion deficit. This has been highlighted in a limited fashion in other studies. Engstrand et al found in their prospective study of ninety patients undergoing limited fasciectomy that although patients have recovered enough composite range of motion for a functional arc of motion, an impairment of finger flexion was still present 12 months after surgery.[154] Few other studies have reported on the impact of surgery on finger flexion and they range from full improvement within two weeks to deficits present six weeks after surgery.[155,156] In our study, patients still had an average of two centimeters of residual tip to palmar crease distance at the three months follow up, which further supports the notion of postoperative stiffness as a result of limited fasciectomy procedures. Patients undergoing this procedure should be counselled preoperatively of the risk of postoperative stiffness, specifically as it relates to a reduction in digit flexion.

In the distal radius cohort, hand edema showed a more linear decline over the course of this study. Interestingly, even at the first follow up two weeks after surgery, water displacement and figure of eight measurements were less than the measured

preoperative values. This outlines the large degree of swelling caused by the initial trauma and fracture, and perhaps suggests that surgical insult may have less impact on hand volume than anticipated. Alternatively, patients on average had surgery roughly one week after the decision for surgery was made and preoperative measurements were taken. Additively, the first postoperative follow up did not occur until two weeks after surgery, which collectively may have resulted in overlooking any acute additional surge in hand edema induced by surgery. Further investigation is required to delineate this concept. However, to our knowledge this data provides new insight on the trajectory of hand swelling after distal radius surgery and can serve as useful reference values for larger clinical investigations.

When evaluating correlation to outcome measures, we found a strong correlation between water displacement and PRWHE in the distal radius cohort. More specifically, water displacement had a stronger correlation with pain scores compared to functional scores when independently analyzed from the PRWHE. Although PRWHE and pain scores after distal radius fractures have been well studied,[157–159] this study provides some objectively evidence about the clinical link between swelling and pain. The degree of this association requires further investigation and our findings suggest that water displacement measurements may be the most useful tool to assess this.

Our study was also able to provide useful data and establish a feasible protocol for a larger RCT evaluating the effects of tranexamic acid on hand and wrist edema. The recruitment rate in our study satisfied our initial goal of five patients per month; however, we experienced a 65% exclusion rate in the distal radius cohort and 29% in the Dupuytren's cohort. The large number of exclusions in the distal radius cohort were mainly related to drug label recommendations or patient refusal. This highlights the potential challenges with recruitment using a drug that is unfamiliar to patients and has a number of contraindications. The preoperative dose administration timing was also variable and suboptimal. This is of arguable importance, however. The timing of the pre-incision administration of TXA is quite variable within the literature. A meta-analysis by Heyns et al suggested most surgical specialties administer TXA within thirty minutes of

skin incision, but this does not appear to be based on any specific science.[160] The threshold for twenty minutes in this study was based on some previous literature and in consultation with our inpatient pharmacists. Although the average in the distal radius cohort approached this threshold, the average administration time relative to the incision in Dupuytren's group was close to one hour. In our protocol, one of the surgical team members administered the preoperative TXA dose in the preoperative anaesthesia block room. This simplified and streamlined the protocol but exposed the timing to notable delays and disruption because they also had other clinical tasks to complete. To allow for an improved, standardized administration we would recommend starting the infusion of preoperative TXA in the operating room prior to skin incision. Otherwise, our protocol seemed to have favorable uptake and feasibility from patient retention, outcome collection, patient feedback and examiner feedback.

This study has a number of limitations. We were unable to recruit the desired sample size established prior to study commencement. Delays in ethics approval and COVID-19 restrictions hampered our ability for efficient recruitment and completion of the protocol. Nonetheless, as a feasibility study, we feel the publication of these results will be beneficial for deciding sample size, measurement tools and study design for future clinical trials surrounding this topic. Although, the volume measurements were mostly completed by a single examiner, there were occasions in which follow up measurements were completed by other study team members. Although every effort was used to standardize the environment including temperature, equipment set up and hand positioning; the rate of hand descent, incomplete descent of the hand and dripping were not overtly controlled. These factors can affect the overall readings. Also, postoperative hand therapy was directed by our centre's hand therapists. All patients were assessed and started therapy in a standardized time point, however, the therapy sessions were not timed, monitored or standardized. They were tailored to each individual patient and patients were not questioned on their commitment to hand therapy at subsequent follow up visits. These factors provide realistic data from common clinical scenarios but can indeed induce variability into the outcome measurements.

Overall, this study was able to provide new insight on acute hand edema after surgery. The data collected in this study can be used as a rubric for larger clinical trials in which acute postoperative hand edema is investigated. It has also provided a protocol that successfully investigated the effects of tranexamic acid on hand and wrist swelling after surgery, a novel use of this medication. This pilot study would suggest that a multicentre randomized clinical trial comparing tranexamic acid with placebo in postoperative hand and wrist edema is feasible.

Chapter 3: Thesis Conclusion

3.1 SUMMARY OF RESULTS AND SIGNIFICANCE

The purpose of this work was to review the current literature pertaining to the formation, evaluation and treatment of hand and wrist edema after surgery. It also served to review the current literature of tranexamic acid and express the notable trends in its use to prevent edema in surgical specialities. This foundational knowledge served as the impetus for the main body of work:

- To objectively define acute hand and wrist edema after surgery
- To assess the relationship of acute postoperative hand and wrist edema with clinical and patient reported outcome measures
- To evaluate the feasibility of a randomized controlled trial involving tranexamic acid in hand and wrist surgery

Hand and wrist edema was evaluated following limited fasciectomy and distal radius fractures. It was hypothesized that patients would experience a surge of hand edema after surgery in both cohorts, with a gradual decline towards normal volume at the final follow up. This was based on the rationale that a surgical insult often causes bleeding and a release of cytokines which can cause a proinflammatory environment, causing resultant edema. We also did expect some of the initial swelling in the distal radius cohort would be from the initial fracture trauma itself. With standard hand therapy, this cumulative visual edema often diminishes overtime. The results of the study, however, showed that even at the first postoperative follow up the degree of swelling was either not significant or significantly decreased. The limited fasciectomy cohort did not demonstrate significant hand and wrist edema throughout the postoperative phase. The distal radius cohort had progressive decline of edema beginning at the first follow up. By the final follow up at three months, hand edema had returned to near comparable values to the contralateral hand.

The link between hand and wrist edema and clinical and patient reported outcomes was investigated. Given the small sample size, the analysis was intended to identify trends

to be further investigated in larger clinical trials. It was hypothesized that an increase in hand and wrist edema would result in an increase in pain, reduced range of motion and less patient function. The limited fasciectomy group did not demonstrate a link between the chosen measurements of hand edema and outcome measurements. Perhaps the most notable finding from this study group, however, was the reduction in full finger flexion at final follow up for this cohort. The distal radius cohort provided a more intriguing connection between water displacement evaluation of hand edema and postoperative pain at multiple follow ups. The strength and degree of this association should be evaluated in larger clinical trials.

This thesis also included a randomized controlled trial to assess the feasibility of its protocol for a larger, multicentred study investigating the effects of tranexamic acid on hand and wrist swelling following surgery. The protocol involved a two-dose intravenous regime of tranexamic acid paired with a matching placebo cohort. The protocol's feasibility was assessed, and outcome measures were analyzed for preliminary tendencies. The protocol developed for this study was successful in most facets desired. The main challenge was the timing of the preoperative dose, which should be amended in future trials. Otherwise, patient recruitment, retention and outcome measurements all satisfied the goals established prior to study commencement. To our knowledge, this was the first trial to use tranexamic acid in an attempt to modulate hand and wrist edema following hand and wrist surgery. This study supports that a larger clinical trial powered to investigate its effects would be feasible.

3.2 IMPACT AND FUTURE DIRECTIONS

Hand and wrist edema has been studied in both the subacute phase and as it relates to lymphedema. However, literature describing acute postoperative hand and wrist edema is sparse. To our understanding, this study is one of the first to bridge the knowledge gap that exists between normal, preoperative hand volume and the establishment of subacute and chronic hand and wrist edema. It assessed patients at multiple time points early after surgery to provide novel reference data as it relates to hand and wrist edema. This naturally lays the groundwork for larger, multicentered trials investigating hand and wrist edema. From the new reference data obtained in this study, trials investigating causes or treatments of early postoperative hand and wrist edema can be implemented. Interestingly, this also broadens the perspective of edema in distal radius fractures, particularly. In our study, we showed that surgical insult in this cohort did not provide a significant additive contribution to overall hand and wrist edema. This may direct future studies to initiate investigations or treatments related to edema in distal radius fractures at the time of injury rather than during surgery. Having reference data also enables physicians and therapists to counsel patients. It allows for comparisons to the normal course and decisions regarding therapy.

It is also possible to continue this trial using the study protocol and increase our sample size numbers. The study was successful in assuring the feasibility of our developed protocol and can be used to springboard a larger, multicentered clinical trial that is powered to investigate tranexamic acid's effects on hand and wrist surgery in depth. This will allow for a stronger analysis and conclusions of the data.

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APPENDIX A: Glossary of Terms

ACUTE   A sudden onset

ANTAGONIST   A substance that interferes with or inhibits the physiological action of another

ARCHIMEDES   A Greek mathematician, physicist, engineer, astronomer, and inventor from the ancient city of Syracuse in Sicily

ARTERIAL   Relates to the muscular-walled tubes forming part of the circulation system by which blood (mainly that which has been oxygenated) is conveyed from the heart to all parts of the body

ARTHROPLASTY   The surgical reconstruction or replacement of a joint

CAPILLARY   Any of the fine branching blood vessels that form a network between the arterioles and venules

CARPUS   A catchall term for all the small bones that connect the wrist and finger bones

COAGULATION   The action or process of a liquid, especially blood, changing to a solid or semi-solid state

CONTRAINDICATIONS   Something (such as a symptom or condition) that makes a particular treatment or procedure inadvisable

COHORT   A group of people banded together or treated as a group

COMORBIDITIES   A disease or medical condition that is simultaneously present with another or others in a patient

CRYOPRESS   A device that delivers extreme cold in medical treatment

DISTAL	Situated away from the centre of the body
DUPUYTREN'S	An abnormal thickening of the skin in the palm of your hand at the base of your fingers
EDEMA	The medical term for swelling
ELECTROGONIOMETRY	The process of using an electrical device used to assess the flexibility and mobility of a joint
EMPIRICAL	Based on, concerned with, or verifiable by observation or experience rather than theory or pure logic
ENDOTHELIAL	A thin membrane that lines the inside of the heart and blood vessels
EXTRACELLULAR	Situated or taking place outside a cell or cells
EX-VIVO	Outside of the living body
FASCIECTOMY	A surgical procedure to remove a layer of tissue called fascia that lies deep under the skin
FEASIBILITY	An assessment of the practicality of a proposed plan or project
FIBROPLASIA	The growth of fibrous tissue, as in wound healing or in certain diseases

FILTRATION	The action or process of filtering
GLOMERULAR	Relating to a cluster of nerve endings, spores, or small blood vessels, especially around the end of a kidney tubule
HEMOGLOBIN	A red protein responsible for transporting oxygen in the blood of vertebrates
HYDROSTATIC	Relating to or denoting the equilibrium of liquids and the pressure exerted by liquid at rest
HYPOXIA	Deficiency in the amount of oxygen reaching the tissues
INTRAVENOUS	Existing or taking place within, or administered into, a vein or veins
IN-VITRO	Performed or taking place in a test tube, culture dish, or elsewhere outside a living organism
IN-VIVO	Performed or taking place in a living organism
INTRAOPERATIVE	Occurring or performed during the course of a surgical operation
ISCHEMIA	A condition in which the blood flow (and thus oxygen) is restricted or reduced in a part of the body

LIGAMENTS	Connective tissue that connects bone to other bone
LYMPHATIC SYSTEM	The network of vessels through which lymph drains from the tissues into the blood
LYSINE	A basic amino acid which is a constituent of most proteins. It is an essential nutrient in the diet of vertebrates
META-ANAYLSIS	examination of data from a number of independent studies of the same subject, in order to determine overall trends.
METACARPAL	Hand bones that are long and slender which connect the carpus to the fingers
OTORHINOLARYNGOLOGY	The study of diseases of the ear, nose, and throat
PERIOPERATIVE	Occurring around the time of surgery
PEROMETER	A device that uses parallel-acting light curtains made of photosensors and light-emitting diodes (LEDs) with which a limb is illuminated and scanned to produce a volume measurement
PRWHE	Patient Rated Wrist and Hand Evaluation: Developed in 1998 for clinical assessment and is used for specific hand and wrist problems

PLACEBO	A substance that has no therapeutic effect, used as a control in testing new drugs
POSTOPERATIVE	During, relating to, or denoting the period following a surgical operation
PREOPERATIVE	Denoting, administered in, or occurring in the period before a surgical operation
PROPHYLACTIC	A medicine or course of action used to prevent disease
PROXIMAL	Situated towards the centre of the body
RADIUS	One of two bones that make up the forearm and wrist joint
RETROSPECTIVE	Looking back on or dealing with past events or situations
RHINOPLASTY	Plastic surgery performed on the nose
SENSITIVITY	Percentage of true positives
SPECIFICITY	Percentage of true negatives
STEREOPHOTGRAMMETRY	Estimating the 3D coordinates of points on an object employing measurements made in two or more photographic images taken from different positions

THROMBOEMBOLIC

Obstruction of a blood vessel by a blood clot that has become dislodged from another site in the circulation

TOPICAL

Relating or applied directly to a part of the body

TRANEXAMIC ACID (TXA)

An antifibrinolytic drug – works by blocking the breakdown of blood clots, preventing bleeding

VASOACTIVE

Affecting the diameter of blood vessels

VENOUS

Relates to any of the tubes forming part of the blood circulation system of the body, carrying in most cases oxygen-depleted blood toward the hear

Health Canada: No Objection Letter

Health   Santé
Canada   Canada

Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator # 3105A
OTTAWA, Ontario
K1A 0K9

05 May 2021

Dr. Ruby Grewal, Canada
c/o Kendrick Au
Orthopaedic Fellow, St. Joseph's Hospital
The Hand and Upper Limb Centre, a division of St. Joseph's Hospital,
an affiliate with Western University
St. Joseph's Health Care London, 268 Grosvenor Street, Room D0-217A
LONDON, Ontario
N6A 4V2
(613) 806-5975

Your file   Votre référence
HC6-24-c250730

Our file   Notre référence

No Objection Letter RE: Protocol # 116724 (Version 6)

Dear Kendrick Au:

I am pleased to inform you that the information and material to support your Clinical Trial Application for **TRANEXAMIC ACID**, control number **250730**, received on April 7, 2021, have been reviewed and we have no objection to your proposed study.

I would remind you of the necessity of complying with the *Food and Drug Regulations,* Division 5, in the sale of this product for clinical testing. In addition, the regulations impose record keeping responsibilities on those conducting clinical trials. You are also reminded that all clinical trials should be conducted in compliance with the Therapeutic Products Directorate's *Guideline for Good Clinical Practice.*

You are reminded of the following requirements:

- Reports for all serious and unexpected Adverse Drug Reactions (ADRs) should be faxed to 613-941-2121 (for therapeutics only).

- All Clinical Trial Notifications should be emailed to hc.oct.ctan-ndec.bec.sc@canada.ca and formatted in accordance with Health Canada's *Guidance Document: Preparation of Drug Regulatory Activities in the "Non-eCTD Electronic Only" Format.*

- A completed Clinical Trial Site Information Form for each Canadian site should be emailed to hc.clinical.trials.site-lieu.essai.clinique.sc@canada.ca prior to initiating the trial at that site.

Consistent with Health Canada's Notice - *Registration and Disclosure of Clinical Trial Information* of November 30, 2007, sponsors are encouraged to register their clinical trials within 21 days of the trial's onset, using a publicly available registry that conforms with international standards for registries such as:

- Clinicaltrials.gov (www.clinicaltrials.gov)
- Current Controlled Trials (www.controlled-trials.com)

Should you have any questions concerning this letter, please contact the Office of Clinical Trials (613) 941-2132.

Sincerely,
This document has been signed electronically using the Health Canada docuBridge system.

Larissa Lefebvre
Manager, Submission Management Division
Office of Clinical Trials

LL/mw

Canada

Ethics Approval

Western Research

Date: 2 June 2021

To: Dr. Ruby Grewal

Project ID: 116724

Study Title: The Role of Tranexamic Acid in Reducing Postoperative Hand Edema After Hand and Wrist Surgery (THAW): A Prospective, Randomized Controlled, Double-Blinded Pilot Study

Application Type: HSREB Initial Application

Review Type: Delegated

Full Board Reporting Date: 22/June/2021

Date Approval Issued: 02/Jun/2021 11:34

REB Approval Expiry Date: 02/Jun/2022

_____

Dear Dr. Ruby Grewal

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. **All other required institutional approvals and mandated training must also be obtained prior to the conduct of the study.**

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Adverse Event Form	Other Data Collection Instruments		
Telephone script_THAW	Telephone Script		
THAW Measurements V2	Other Data Collection Instruments		
THAW PRWHE V2	Paper Survey		
NRS THAW	Paper Survey		
Baseline patient demographic THAW V2	Paper Survey		
TxA (THAW) Protocol V6 REB	Protocol	29/Apr/2021	6
THAW LOI & Consent V7	Written Consent/Assent	31/May/2021	7
THAW Recruitment Check List V2	Other Data Collection Instruments		

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Omega TXA - PRODUCT MONOGRAPH	Product Monograph		
No Objection Letter - Health Canada	NOL/NOA/ITA		

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

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

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

Curriculum Vitae: Kendrick Au

KENDRICK D. AU, BSc MD FRCSC

EDUCATION

2020-Present   **Hand and Upper Extremity Fellowship (Expected end date: July 31, 2022)**
Roth-McFarlane Hand and Upper Limb Center, London ON

2020-Present   **Master of Science, Surgery (Expected end date: May 2, 2022)**
Candidate, University of Western Ontario
Supervisors: Dr. Ruby Grewal, Dr. Douglas Ross, Dr. Joy MacDermid

2015- 2020   **Orthopaedic Surgery Residency Program**
Division of Orthopaedic Surgery, University of Ottawa and The Ottawa Hospital, Ottawa, ON

2011-2015   **Doctor of Medicine**
Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL

2007-2011   **Bachelor of Science (*Biology, Premed*)**
Brown University, Providence, Rhode Island, USA

ACADEMIC HONORS AND AWARDS

2020   **Resident Teaching Award – Division of Orthopaedic Surgery, University of Ottawa**
Selected by residents in the Division of Orthopaedic Surgery for excellence in clinical teaching

2018   **Hans Uhthoff Research Day – Division of Orthopaedic Surgery, University of Ottawa**
First place: "A Biomechanical Analysis of the DRUJ Ballottement Test"

2016   **Hans Uhthoff Research Day – Division of Orthopaedic Surgery, University of Ottawa**
Third place: "Predicting hospital length of stay and short-term function after hip or knee arthroplasty: are both performance and comorbidity measures useful?"

2016   **Guardian Angel Award - The Ottawa Hospital Foundation**
A patient driven donation to show appreciation and recognize exceptional care

2015   **Rich Fagan Award in Orthopaedic Surgery - Memorial University of Newfoundland**
For outstanding achievements in the discipline of Orthopaedic Surgery during clerkship

2011   **ITA/Arthur Ashe Leadership and Sportsmanship Award – Division I Northeast Region**
Recognizes college tennis players who have exhibited outstanding sportsmanship and leadership as well as scholastic, extracurricular and tennis achievements.

2011   **Academic All-Ivy Award – Brown University, Providence, RI, USA**
Recognizes high achievements in both sport and academics

2011   **Brown University's Dave Zucconi Award - Brown University, Providence, RI, USA**
Recognizes sportsmanship and fair play

PROFESSIONAL MEMBERSHIPS

2020-present   **Royal College of Physicians and Surgeons of Canada**

2015-present   College of Physicians and Surgeons of Ontario
2015-present   Canadian Orthopaedic Association
2015-present   Canadian Medical Association
2015-present   Ontario Medical Association
2015-present   American Academy of Orthopaedic Surgeons

COMMITTEES AND POST-GRADUATE TEACHING EXPERIENCE

2020-Present   Western University Orthopaedic Surgery Program - Teaching rounds and half-day, educator
2017-2019   Ontario's Workers Network (OWN) - Workplace Safety and Insurance Board (WSIB), developer
2016-2020   University of Ottawa Medical School – Anatomy and surgical skills, instructor
2015-2020   Resident Mentorship Program - Division of Orthopaedics, University of Ottawa
2016-2020   Ottawa Senators Foundation - Participant
2016-2019   Principles of Surgery - Instructor, University of Ottawa
2015-2019   Orthopaedic Surgery Interest Group - University of Ottawa
2015-2016   CUSP Committee - Civic Campus, The Ottawa Hospital

PUBLICATIONS

Peer Reviewed Articles
Poitras S, **Au K**, Wood K, Dervin G, Beaulé PE. Predicting hospital length of stay and short-term function after hip or knee arthroplasty: are both performance and comorbidity measures useful? *Int Orthop.* 2018 PMID: 29453585 DOI: 10.1007/s00264-018-3833-y

Undurraga S, **Au K**, Dobransky J, Gammon B. Scaphoid Excision and Bicolumnar Carpal Fusion with Retrograde Headless Screws. *J Wrist Surg,* 2020. PMID: 34109062 DOI: 10.1055/s-0040-1721853

Book Chapters
Au K, Grewal R. "Fractures and Dislocations of the Carpus." *AAOS Resident Curriculum,* 2020. Edited by Ring D, Adams J

Au K, Suh, N. "Tendon Injuries and Tendinopathies of the Hand and Wrist." *AAOS OKU14, 2021.*

CURRENT RESEARCH

2020-present   Au K, Grewal R, Ross D, MacDermid J. "The Role of Tranexamic Acid in Reducing Postoperative Hand Edema After Hand and Wrist Surgery (THAW): A Prospective, Randomized Controlled, Double-Blinded Pilot Study"

2016-present   Au K, Culliton K, Undurraga S, Louati H, Gammon B "A Biomechanical Analysis of the DRUJ Ballottement Test"

2016-present   Au K, Culliton K, Undurraga S, Louati H, Gammon B "A Biomechanical Comparison of Dynamic CT Scan and Stress CT Scan for DRUJ Instability"

RESEARCH GRANTS

2021-present   Department of Surgery IRF - The Role of Tranexamic Acid in Reducing Postoperative Hand Edema After Hand and Wrist Surgery (THAW): A Prospective, Randomized Controlled, Double-Blinded Pilot Study.

CONFERENCE PRESENTATIONS

A Biomechanical Analysis of the DRUJ Ballottement Test: **Au K**, Culliton K, Undurraga S, Louati H, Gammon B
Poster presentation: COA 2019, Hans Uhthoff research day (1st place, 2019)

A Biomechanical Comparison of Dynamic CT Scan and Stress CT Scan for DRUJ Instability: **Au K**, Culliton K, Undurraga S, Louati H, Gammon B
Podium presentation: COA 2020

Midterm results of Scaphoid Excision and Bicolumnar Carpal Fusion Using Retrograde Headless Screws: Undurraga S, **Au K**, Dobransky J, Gammon B
Podium Presentation: COA 2019

Predicting hospital length of stay and short-term function after hip or knee arthroplasty: are both performance and comorbidity measures useful?: Poitras S, **Au K**, Wood K, Dervin G, Beaulé PE
Podium Presentation: AAOS 2016, Hans Uhthoff Research day 2016 (Third place)
Poster Presentation: COA 2016

CONFERENCES AND COURSES

2019	**Tribe Medical Hand and Wrist Weekend Course**, Toronto, ON
2017	**AO Trauma Course - Advanced Principles of Fracture Management,** Toronto, ON
2016	**American Academy of Orthopaedic Surgeons Conference,** San Diego, USA, Presenter
2015	**AO Trauma Course - Basic Principles of Fracture Management,** Tampa Bay, USA
2018	**Canadian Orthopedic Association Conference,** Presenter
2016	**Canadian Orthopedic Association Conference,** Poster presentation
2014	**Canadian Orthopedic Association Conference,** Participant

LICENSES AND CERTIFICATIONS

2017	**RCPSC Surgical Foundations**
2017	**MCCQE Part II**
2017	**United States Medical Licensing Exam (USMLE) STEP 2 CS**
2016	**ATLS Certification**
2015	**MCCQE Part I**
2015	**USMLE STEP 2 CK**
2015	**Heart & Stroke Foundation BCLS/ACLS Certification**
2014	**Standard First Aid/CPR/AED**
2013	**Neonatal resuscitation**