8-28-2020

Botulinum Injection in the Tensor Fasciae Latae as an Adjunct Treatment for Iliotibial Band Syndrome

J. Morgan Jones
Yale Physician Associate Program, jmorgan.jones@yale.edu

Botulinum Injection in the Tensor Fasciae Latae as an Adjunct Treatment for Iliotibial Band Syndrome

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Masters in Medical Science

August 2020

J. Morgan Jones, PA-SII
Class of 2020
Yale Physician Associate Program

Michael Medvecky, MD
Associate Professor of Orthopedics and Rehabilitation
Section Chief of Sports Medicine

Table of Contents

Abstract

Iliotibial band syndrome is a highly prevalent and painful condition characterized by anterolateral knee pain from an inflamed iliotibial band, with the current standard of care being physical therapy. However, we lack sufficient adjunct treatment options for patients with refractory iliotibial band syndrome who fail physical therapy. **This study will evaluate the efficacy and safety of using botulinum toxin type A injections into the tensor fasciae latae as an adjunct therapy for patients with refractory iliotibial band syndrome.** With all patients receiving the same physical therapy treatment, we randomized patients to the control group of saline injection and to the treatment group of botulinum toxin type A injection. Successful use of botulinum injections will lead to significant improvement in pain and function in patients with refractory iliotibial band syndrome and open the door for its use in other muscle imbalance syndromes.

Chapter 1 – Introduction

Background

Incidence and Prevalence

Iliotibial band syndrome (ITBS) is a painful and aggravating condition commonly found in physically active individuals. ITBS is a syndrome of overuse and is highly prevalent amongst athletes and military personnel[1-3]. ITBS is considered to be the most common overuse injury of the lateral knee with incidence ranging between 2 and 12%, and higher rates noted in active individuals such as runners, cyclists, soccer players, and military recruits[,4-6]. Among cyclists, the prevalence of ITBS has been reported between 15-24%[7]. In a study on female college athletes, including field hockey, soccer, and basketball players, Devan et al. (2004) demonstrated ITBS to be the most common overuse injury of the lower extremity[8]. ITBS has also been noted to be a common cause of lateral knee pain in rowers, hockey players, triathlon runners, and skiers[8-10].

Anatomy

The iliotibial band (IT band) is a fibrous sheath that runs vertically from the iliac crest, along the lateral aspect of the thigh, to the lateral proximal tibia. It functions as both a tendon, connecting bone to bone, and a ligament, connecting muscle to bone, thereby connecting and stabilizing a multitude of vital structures in the proximal leg. The IT band is a fibrous reinforcement of the tensor fasciae latae (TFL) and originates from the external lip of the iliac crest on the iliac tubercle. Proximally, the IT band attaches to the TFL gluteus maximus, gluteus minimus, and vastus lateralis and runs across the greater trochantic bursa. Distally, the IT band

connects to lateral femoral epicondyle, quadriceps-patella-patellar tendon complex, and the biceps femoris muscle tendon-fibula complex. The IT band attaches to the lateral femoral epicondlye via the patellar retinaculum and epicondylo-patellar ligament. The final insertion point of the IT band is at Gerdy's tubercle on the anterolateral tibia[2,3,11].

One of the predominant muscles the IT band emerges from is the TFL. The TFL is a fusiform muscle that originates from the anterior superior iliac spine and the anterior iliac crest. It is enclosed between two layers of the fasciae lata and, in combination with the gluteus maximus, merges into the iliotibial band, serving as its attachment proximally. The TFL is an accessory muscle with its main role being in medial hip rotation and hip abduction, while also contributing to stability of the knee during flexion and extension[1,5,11].

Biomechanics

The purpose of the IT band is not only to contribute to lateral knee stabilization, but also help coordinate movements of its associated muscles to abduct, extend, and laterally rotate the hip. In active flexion of the knee, the IT band sits posteriorly to the lateral femoral epicondyle and assists in knee flexion. In full extension, the IT band moves anterior to the lateral femoral epicondyle and acts as an active knee extensor. It is this motion of the IT band gliding over the lateral femoral epicondyle with knee flexion and extension that is the proposed mechanism for IT band associated knee pain[1,2,4,12].

Pathogenesis

ITBS occurs from overuse and is not considered a traumatic injury. It is characterized by anterolateral knee pain associated with the distal IT band. However, the exact pathogenesis of this pain is still is unknown. As we know this is a syndrome of overuse, it is safe to assume the etiology of the pain is associated with increased movment of the IT band and its associated distal anatomy. Originally, it was thought to be a direct tendonitis due to friction irritation of the IT band gliding over the lateral femoral epicondlye, and was therefor perviously termed "iliotibialband friction syndrome"[13]. More recent investigation has realitivly disproved this theory, demonstrating that the IT band is stongly teathered to the lateral femoral epicondlye, and does not demonstrate sufficient movment to cause friction and inflamed distal ITB[14].

One of the more recent predominant theories, was that of an IT band bursitis of the lateral femoral epicondyle bursa. This theory suggests that the increased rubbing of the IT band over the lateral femoral epicondyle bursa causes inflammation of the bursa and therefor pain[5]. However, flaws have also been associated with this theory. Recent cadaver, MRI, and ultrasound studies have illustrated that there is no directly associated bursa deep to the IT band at the lateral femoral epicondlye[14,15]. The most recent data suggest that the anteriolateral knee pain may be associated with vascular and innervated adipose tissue deep to the IT band, or compression at the lateral synovial recess[14].

While the exact pathogenesis of IT band syndrome is still unclear, we do know that the pathogenesis results from overuse and is associated with decreased IT band flexibility and signature anteriolateral knee pain. A reduction in IT band length and increase in recruitment of accessory muscles, such as the TFL, has been noted in patiets with IT band syndrome and is theorized to contribute to the pathogenesis of this syndrome[1,4,5]. From the current data, it is

reasonable to work off the hypothesis that IT band syndrome results from increased knee extension and flexion resulting in a reduction in length of the IT band and irritation to the anteriolateral knee. Risk factors for developing ITBS include intense cross training, distance running, cycling, decreased ITB length, and weakness in the muscles of the knee extensors, flexors, and hip abductors[4,11,12].

Diagnosis

Patient history and physical exams are often all that are needed to make the diagnosis of ITBS. Characteristic anterolateral knee pain localized between the lateral femoral epicondyle and Gerdy's tubercle is highly indicative for ITBS. This pain is usually brought on by repetitive extension and flexion exercises of the knee. Three physical exam maneuvers are commonly employed to diagnose ITBS; the Noble, the modified Ober, and Thomas test. These physical exam maneuvers, coupled with a fitting patient history, are highly indicative and oftentimes diagnostic for ITBS[2,3,11,12].

In the Noble test the patient lays supine and the provider flexes and extends the knee several times from 0-90° while applying pressure to the lateral epicondyle of the femur. Pain or crepitus is considered a positive Noble's sign, which is indicative for an irritatted distal IT band. For the modified Ober test, the patient lies on their unaffected side with their unaffected leg flexed at the hip and knee. The examiner places one hand on the superior hip to stabilize the pelvis and the uses the other to flex the knee to 90° while keep the thigh at 0°. If the thigh fails to fall more than 10° from neutral, it is considered a positive modified Ober test, and in indicative of IT band and TFL tightness[16]. Finally, the Thomas test is used to measure the general flexibility of hip flexors including iliopsoas muscle group, the rectus femorus, gracilis, and TFL.

In the Thomas test, the patient lies supine and the patient flexes both of their hips and knees, pulling the legs as far into the torso as possible. The patient then releases and extends the affected leg; the test is considered positive if the patient's posterior thigh cannot reach the table and indicated overall hip flexor tightness[4].

Imaging is not needed to diagnose ITBS but is often employed to rule out other knee pathologies such as arthritis, joint space narrowing, patellar tracking abnormalities, and fractures. Plain film X-rays will read as normal or benign in patients with ITBS[2,3,11]. MRI can be useful in patients with chronic ITBS, as it can demonstrate inflammation and thickening of the IT band with possible associated fluid buildup over the lateral epicondyle[17]. However, fluid build up over the lateral epicondyle has been demonstrated to be non-specific and non-diagnostic to ITBS[15.] MRI is also useful in chronic ITBS patients as it helps rule out other knee pathologies as a source of the patient's pain, such as tendon and meniscal tears, cartilage degeneration, and cysts.

Current Treatment Options

The current standard of care for ITBS is conservative treatment that consists of rest for athletic activities with gradual return to activity as tolerated. This activity restriction is commonly coupled with physical therapy and NSAID use. Physical therapy for ITBS is generally focused on hip abductor and knee extensor strengthening, and ITB stretching and lengthening[11]. Although there is a wide array of specific treatment plans for acute ITBS, the most effective treatment regimens all involve a combination of rest, ice, physical therapy, NSAIDs[2,3]. For those who fail traditional conservative treatment of rest and physical therapy, the next steps in ITBS management are corticosteroid injection for symptom relief and diagnosis, and possible surgical release of the IT band. Surgery is considered a final line of therapy for those with refractory or

chronic ITBS, but is not always a viable option for patients as it comes with its own set of increased risks and cost[3,18].

Statement of the Problem

While rest and physical therapy have been demonstrated to be very effective treatment options for acute ITBS, few good treatment options exist for those who fail physical therapy. The few alternate therapies available such as steroid injections or surgical release, come which come with their own unique set of risks and expenses. This leaves a gap in care for those patients who continue to have chronic pain and therefore demonstrates a need for new therapeutic options. In particular, athletes and active young adults are at higher risk for developing chronic ITBS, as their lifestyle is not conducive to standard conservative treatment guidelines. We are in need of new adjunct therapies for these patients with refractory pain, who without better adjunct treatment options, will continue to experience pain or opt for surgical intervention that may carry more risks than benefits.

Goals and Objectives

The purpose of our study is to investigate alternative adjunct therapies for anterolateral knee pain associated with ITBS. Our proposed intervention of non-surgical release of the tensor fasciae latae via botulinum toxin type A (BT) injection coupled with standard physical therapy will aid in the lengthening of the IT band and hopefully improve therapeutic outcomes. We will be specifically looking at self-reported knee pain improvement measured with the Anterior Knee Pain Scale (AKPS) as our primary outcome, as well as functional improvement and IT band length as secondary outcomes. Information gained from this study will lead to new insight into treatment options for musculoskeletal pain and adjunct treatments for ITBS and other muscle

imbalance syndromes. Successful use of BT injections as an adjunct treatment for ITBS will improve overall pain and function of patients, reduce need for surgical intervention, and reduce the prevalence of chronic ITBS. In addition, successful treatment of ITBS with BT will open the door for the use of BT in other musculoskeletal pain syndromes.

Hypothesis

In adults with chronic ITBS, adjunct therapy of a one time .75 units BT in 4mL saline injection into the TFL, coupled with physical therapy, will have a significant reduction in anterolateral knee pain at 6 months, measured with the Anterior Knee Pain Scale, when compared to placebo group, who will receive one 4mL injection of saline into the TFL and physical therapy.

Definitions

Adults: Patients ages 18-55.

Chronic ITBS: Iliotibial band syndrome for greater than 6 months, with at least one attempt of conservative standard of care physical therapy for greater than two months.

Treatment Group: Patients randomized to receive a one-time .75units of BT in 4mL saline injection into the TFL coupled with standard of care physical therapy.

Placebo Group: Patients randomized to receive a one-time 4mL injection of saline into the TFL coupled with standard of care physical therapy.

Anterior Knee Pain Scale (AKPS): assesses subjective symptoms as well as functional limitations surrounding knee pain; it is a well-validated 13 question self-assessment focused on anterior knee pain with a scoring scale of 0-100, 0 being no symptoms[19].

Chapter 1 Citations

1. Baker RL, Fredericson M. Iliotibial Band Syndrome in Runners: Biomechanical Implications and Exercise Interventions. *Phys Med Rehabil Clin N Am.* 2016;27(1):53-77.

2. Kirk KL, Kuklo T, Klemme W. Iliotibial band friction syndrome. *Orthopedics.* 2000;23(11):1209-1214; discussion 1214-1205; quiz 1216-1207.

3. Strauss EJ, Kim S, Calcei JG, Park D. Iliotibial band syndrome: evaluation and management. *J Am Acad Orthop Surg.* 2011;19(12):728-736.

4. Fredericson M, Cookingham CL, Chaudhari AM, Dowdell BC, Oestreicher N, Sahrmann SA. Hip abductor weakness in distance runners with iliotibial band syndrome. *Clin J Sport Med.* 2000;10(3):169-175.

5. Messier SP, Edwards DG, Martin DF, et al. Etiology of iliotibial band friction syndrome in distance runners. *Med Sci Sports Exerc.* 1995;27(7):951-960.

6. Taunton JE, Ryan MB, Clement DB, McKenzie DC, Lloyd-Smith DR, Zumbo BD. A retrospective case-control analysis of 2002 running injuries. *Br J Sports Med.* 2002;36(2):95-101.

7. Holmes JC, Pruitt AL, Whalen NJ. Iliotibial band syndrome in cyclists. *Am J Sports Med.* 1993;21(3):419-424.

8. Devan MR, Pescatello LS, Faghri P, Anderson J. A Prospective Study of Overuse Knee Injuries Among Female Athletes With Muscle Imbalances and Structural Abnormalities. *J Athl Train.* 2004;39(3):263-267.

9. Rumball JS, Lebrun CM, Di Ciacca SR, Orlando K. Rowing injuries. *Sports Med.* 2005;35(6):537-555.

10. Tuite MJ. Imaging of triathlon injuries. *Radiol Clin North Am.* 2010;48(6):1125-1135.

11. Baker RL, Souza RB, Rauh MJ, Fredericson M, Rosenthal MD. Differences in Knee and Hip Adduction and Hip Muscle Activation in Runners With and Without Iliotibial Band Syndrome. *Pm r.* 2018;10(10):1032-1039.

12. Pegrum J, Self A, Hall N. Iliotibial band syndrome. *Bmj.* 2019;364:l980.

13. Hariri S, Savidge ET, Reinold MM, Zachazewski J, Gill TJ. Treatment of recalcitrant iliotibial band friction syndrome with open iliotibial band bursectomy: indications, technique, and clinical outcomes. *Am J Sports Med*. 2009;37(7):1417-1424.

14. Fairclough J, Hayashi K, Toumi H, et al. The functional anatomy of the iliotibial band during flexion and extension of the knee: implications for understanding iliotibial band syndrome. *J Anat*. 2006;208(3):309-316.

15. Jelsing EJ, Finnoff J, Levy B, Smith J. The prevalence of fluid associated with the iliotibial band in asymptomatic recreational runners: an ultrasonographic study. *PM R.* 2013;5(7):563-567.

16. Stephen JM, Urquhart DW, van Arkel RJ, et al. The Use of Sonographically Guided Botulinum Toxin Type A (Dysport) Injections Into the Tensor Fasciae Latae for the Treatment of Lateral Patellofemoral Overload Syndrome. *Am J Sports Med.* 2016;44(5):1195-1202.

17. Ekman EF, Pope T, Martin DF, Curl WW. Magnetic Resonance Imaging of Iliotibial Band Syndrome. *The American Journal of Sports Medicine.* 1994;22(6):851-854.

18. Inoue H, Hara K, Arai Y, et al. Outcome of Low-Invasive Local Split-Thickness Lengthening for Iliotibial Band Friction Syndrome. *Int J Sports Med.* 2018;39(3):232-236.

19. Ittenbach RF, Huang G, Barber Foss KD, Hewett TE, Myer GD. Reliability and Validity of the Anterior Knee Pain Scale: Applications for Use as an Epidemiologic Screener. *PLoS One.* 2016;11(7):e0159204.

Chapter 2 – Review of the Literature

Introduction

A comprehensive review of the literature was conducted utilizing PubMed, Cochrane Library, Emabse, Scopus, Clinicaltrials.gov, and Ovid Medline. The controlled vocabulary terms searched for were "iliotibial band," "iliotibial band pain syndrome," "botulinum toxin," and "anterolateral knee pain." For a wider look and comprehensive review, the key words "Botox," "Dysport," "knee pain," "IT band," "tensor fasciae latae," "runner's knee," "patellofemoral overload syndrome," and "iliotibial band friction syndrome" were also searched for. The results of this extensive search of the literature further enhance the need for this study while also illustrating the basis for this study's design.

Review of Empirical Studies About the Relationship Being Studied

Iliotibial Band Syndrome

Iliotibial band syndrome is thought to be a syndrome of overuse. It involves weakened hip flexor muscles and an overactive tensor fasciae latae, with repeated movements leading to inflammation and pain of the distal iliotibial band[1-3]. In a case series study by Fredericson et al. (2000) the authors compared the hip abductor torque of 24 runners with ITBS to 30 control runners. At baseline, there was a statistically significant difference in hip abductor torque between the control and ITBS group ($p < 0.05$). The ITBS group then completed 6 weeks of physical therapy focused on hip abductor strengthening, at the end of which females

demonstrated a 34.9% increase in hip abductor torque and males a 51.4% increase in hip abductor torque. 22 out of 24 participants with ITBS were pain free after 6 weeks and were able to return to athletics[4]. This study supports the theory that ITBS is associated with weak abductor muscles, and demonstrates hip abductor strengthening to be a curtail component in treatment.

In an observational cross-sectional study by Baker et al. (2018), 15 injured runners with iliotibial band syndrome were compared with 15 control runners to examine the frontal knee and hip kinematics in patients with iliotibial band syndrome. Data was collected on a 30-minute run via a three-dimensional, high-speed camera synchronized with wireless surface electromyography. They demonstrated that runners with iliotibial band syndrome had increased knee adduction and valgus alignment (P = .002, control = -1.48°, injured = 3.74°) and increased tensor fasciae latae muscle activation (P = .017, control = 7% maximal contraction, injured = 11% maximal contraction)[5]. This study offers support to the theory that ITBS is due in part to weakened hip muscles and overcompensation of the tensor fasciae latae. Therefore, this biomechanical theory of ITBS also offers rationale to the hypothesis suggested. The hypothesis that inhibition of the overcompensating tensor fasciae latae, through BT injection, could optimize physical therapy focusing on hip abductor strengthening and IT band stretching.

Botulinum Toxin in Musculoskeletal Disorders

Botulinum toxin works by paralyzing skeletal muscle and has recently been used therapeutically in a wide array of musculoskeletal disorders. Its therapeutic paralytic effects have been demonstrated to be safe and effective in treating disorders such as essential tremor, Parkinson's freezing gait, cervical dystonia, and strabismus[6-8]. Botulinum toxin works by inhibiting the release of acetylcholine at the neuromuscular junction, causing flaccid paralysis.

Safety and efficacy of BT injections specifically into the TFL have been investigated in two studies; one for Parkinson's freezing gate and another for cerebral palsy. Vastik et al. (2016) investigated the use of BT injections into the TFL for 10 Parkinson's freezing gait patients compared to 10 Parkinson's patients without freezing gait who did not receive BT injections. While the results did show that there was a significant decrease in freezing gait symptoms by 3 points ($p < 0.001$), the sample size was very small, and their method of comparison was questionable. Most importantly, the study showed no adverse effects from the BT injection into the TFL, and an increase in accessory muscle recruitment[9]. Brunner et al. (2000) demonstrated the efficacy of BT injections into the TFL for non-surgical release of the IT band in cerebral palsy patients with hip malrotation[10]. Furthermore, BT has become a popular therapeutic option for patients with cerebral palsy and is widely considered a safe and effective technique in combating this musculoskeletal disorder[11].

In Dunne and Singer (2010) investigated the mechanism and safety of BT uses in the VL for muscle imbalance syndrome related knee pain. Looking at the long-term effects of BT injections, this follow up observational study was done to examine the length of denervation of the vastus lateralis following BT injection. This study investigated a sample of convenience from subjects previously enrolled in BT for refractory anterior knee pain studies. 9 women and 1 man, ages 16-25, all of whom had received BT injections into the vastus lateralis for refractory anterior knee pain in previous clinical trials, were enrolled. All 10 patients reported ongoing relief of symptoms at the time of the study, but 2 did ultimately undergo surgical intervention for refractory anterior knee pain. Subjects underwent needle electromyography into the vastus lateralis to quantify muscle denervation post-injection, measured in motor unit potential (MUP). All 10 subjects showed a significant reduction in MUP in the injected leg compared with their

own control non-injected limb, with a mean MUP amplitude reduction of 49% (p=0.0005) and duration reduction 36% (p=0.0003). The extent of muscle abnormality and reduction in MUP demonstrated a dose-dependent correlation and a correlation with time sense injection[12]. While this study was a small sampled observational study, with a sample of convenience leading to a contributing sampling bias, it gives us insight into the long-term effects of BT injections into the vastus lateralis. It encouragingly demonstrates that BT injections are relatively safe and provide lasting effects on muscle denervation, which could be a promising therapeutic benefit.

Botulinum Toxin and Knee Pain

Botulinum toxin has many uses and is continuing to show promise in the treatment of many muscle imbalance syndromes[7,8,11]. Recently researchers have been exploring its use in specific muscle imbalance syndromes of the knee and thigh, namely with patellofemoral pain syndrome, patellofemoral overload syndrome, and iliotibial band syndrome. These studies operate on the theory, that by inhibiting an overactive muscle in the leg with a BT injection, you will allow for more productive physical therapy and therefore a greater decrease in symptoms. Overall these studies have had promising results, demonstrating a general improvement in symptoms with virtually no adverse events or side effects noticed.

Singer et al. (2006) was one of the first to demonstrate the utility of BT injections for treatment of muscle imbalance syndromes and knee pain. In this study, eight women, ages 18-40, with a history of chronic anterior knee pain were given BT injections ranging from 300-500 units into the distal portion of the vastus lateralis, followed by a 12 week at home physical therapy regiment. The goal of this treatment was to enhance vastus medius recruitment and improve knee control, which would lead to an improvement in knee pain and function. Results were examined

through standard CT sequence on the quad, isometric quad strength, and self-reported knee pain and disability (measured with the Knee Injury and Osteoarthritis Outcome scale (KOOS)). At 12 weeks the patients demonstrated no significant increase in vastus medius cross-sectional area but did demonstrate a decrease in vastus lateralis cross-sectional area 12.4% (+5%) (p 5 0.05). Patients also demonstrated an improvement in quadriceps strength as well as knee pain and function improvement[13]. While promising, this study, with only eight female subjects, is not evidence enough to promote the use of BT for anterior knee pain in the general population. In addition, this study offered no control group, therefore we cannot exclude a placebo effect as a confounding variable. Due to the lack of control group, improvements in knee pain could possibly be contributed to physical therapy without any effect from the BT injection; further studies are needed to investigate this relationship. The KOOS scale was demonstrated to not be particularly sensitive in the population studied, as most patients were able to remain active throughout the study. Finally, this study had a relatively short follow-up period of 12 weeks. Further studies will be needed to examine not only the efficacy, but the safety of using BT injections long term. In conclusion, this is a promising pilot investigation, but is lacking sufficient data to demonstrate any true effect.

In 2011 Singer followed up her initial investigational study from 2006 with a double blind, randomized, placebo-controlled crossover trial study, to examine the efficacy of BT injections into the vastus lateralis for patellofemoral knee pain. 24 Patients, ages 15-55, with patellofemoral pain syndrome, clear evidence of vastus lateralis dominance on EMG, and no other structural knee pathologies or injuries, were enrolled in the study. 14 patients were randomized to the treatment group and received 500 units BT in 4 mL saline injections into the vastus lateralis, and the 10 in the control group received 4 mL saline injections into the vastus

lateralis. The theory behind this treatment plan was that inhibition of the overcompensating VL would allow for more effective strengthening of the weakened vastus medius, leading to a correction of the biomechanical muscle imbalance thought to be the cause of these patients' anterior knee pain. Both cohorts received the same physical therapy and were instructed to perform exercises at home twice daily. Patients were followed for 24 weeks with pain and function assessments at 2, 4, 6, 12, and 24 weeks using the Anterior Knee Pain Scale (AKPS). At the initial endpoint of 12 weeks, significant improvement in knee pain from baseline was noted in the BT group over the control ($p < 0.03$). Also, at 12 weeks, 5 subjects from the control group elected crossover and received open-label BT injections. Statistical analysis was not performed on this group due to small sample size. Long term follow-up at 24 weeks demonstrated that the initial BT treatment group showed sustained improvement in 11 out of the 14 subjects[14]. Possible confounding variables include patient's adherence to physical therapy, frequency of NSAID use, extent of previous knee injuries.

Overall, this was a promising follow up study to Singer's initial investigation into the use of BT for patellofemoral knee pain that provided an increased level of evidence through the double-blind placebo-controlled study design. Another promising point in this study was the long term follow up to 24 weeks, which helps to investigate the use of BT not only as a symptomatic treatment but also as a curative measured aimed at preventing the need for surgery. Although, much more extensive follow up with a more detailed data collection and analysis will be needed to support this claim. Finally, the sample size in this study was too small to make these results applicable to the general population. Further studies with larger populations and more thorough follow-up are needed[14].

These promising studies by Singer[13,14] demonstrate promise for the short-term use of BT in treating anterior knee pain caused by muscle imbalance syndromes. For evidence of long-term safety and efficacy we can look at Silbert et al. (2012). This was a follow-up retrospective study: 46 patients from previous clinical trials and 19 patients from private medical clinics who had received the same treatment of a one-time injection of BT into the vastus lateralis for patellofemoral knee pain were surveyed, in an attempt to examine the long-term effects of this treatment. This study was primarily measuring self-reported symptom relief and if knee surgery was required post-injection. They found that a single BT treatment led to an initial improvement in pain and function in 57 out of 65. 44 of those 57 patients who reported initial symptom relief stated that they continued to have long-term treatment benefits for an average of 34 months (SD 25) post-injection[15]. This study only reported the mean treatment benefit length for those who sustained long-term results; they did not expand upon the 8 patients who received no initial benefit and the 13 patients that only received short-term treatment benefits.

The role of BT in the treatment of knee pain associated with patellofemoral syndrome has been supported by numerous other studies[16-18]. Chen et al. (2015) was a prospective case control study for intervention, where 12 patients with bilateral anterior knee pain associated with patellofemoral syndrome received BT injections into the VL of their worse knee and used their non-injected knee as a control. This study demonstrated a significant reduction in anterior knee pain assessed with the WOMAC self-reported knee pain questionnaire ($p<0.05$)[17]. With a small sample size and patients acting as their own control, this study offers a low level of evidence on its own, but offers support to the use of BT for anterior knee pain.

While there is increasing evidence for the use of BT injections in the VL for treatment of knee pain associated with patellofemoral syndrome[13-15,19], only one case series study has been

done to evaluate the safety and efficacy of botulinum toxin type A in the TFL. Stephen et al. (2016) used ultrasound guided botulinum toxin injection into the TFL followed by physical therapy in 45 patients classified as having patellofemoral overload syndrome from either ITBS or superolateral fat pad impingement. Significant improvement in knee pain, measured using the Anterior Knee Pain Scale, and in IT band length, measured via the modified Ober test was demonstrated in 39 out of 45 patients. Symptom improvement in this study is suggested to be due to reduced lateral TFL/ITB tension, leading to increased hip abductor strength via the inhibition of the TFL. Overall, this study illustrates the safety and possible efficacy of using botulinum toxin injections into the TFL as an adjunct therapy for anteriolateral knee pain caused by ITBS. The drawback to this study is that it is designed as a case control and all participants acted as their own control. Therefore, the level of empirical scientific evidence is low, and confounding variables and placebo effect cannot be ruled out. Furthermore, this study focused on the treatment of anterior knee pain categorized as "patellofemoral overload syndrome" caused by either ITBS or superior lateral fat pad impingement, and was not focused on the treatment of ITBS anterior lateral knee pain specifically. This study provides evidence that botulinum toxin could be a viable treatment of ITBS, as it demonstrated a reduction in knee pain and lengthening of the IT band, but further studies are needed to evaluate this hypothesis[20].

Review of Relevant Methodology

Patient Selection

ITBS is a highly prevalent condition frequently seen in orthopedic sports medicine clinics[2]. Therefore, orthopedic sports medicine clinics are an optimal place to recruit participants

for ITBS research. In Fredericson et al. (2000), patients were recruited from an orthopedic runner's injury clinic. They were chosen based on history and physical exam with the prominent symptoms being lateral knee pain, local tenderness over the lateral epicondyle, a positive Noble compression test, and the absence of any other knee injury such as effusion or tendon injury. Patients were excluded if they had any history of previous knee trauma, surgery, or other abnormal knee findings[4]. The history and physical exam findings used as selection criteria for this study are quite specific and reliable techniques for isolating patients with ITBS, but they lacked the use of imaging for more definitive diagnoses.

Baker et al. (2018) recruited patients by either referral from a local running club or orthopedic clinics, and utilized similar inclusion criteria at Fredericson et al. (2000) for isolating patients with ITBS for their study. They also relied on the Noble compression test as a key diagnostic factor for ITBS, and excluded patients if they had signs of any other knee injury other than ITBS. One inclusion criteria specific to this study was that all their participants had to run at least 10 miles per week before injury[1]. While this is a good inclusion criteria when specifically studying runners, it limits the patient population considerably. Inclusion criteria and recruitment techniques for the study being proposed will include components of these two studies, including the recruitment from sports medicine clinics and the utilization of the Noble test as an inclusion criteria.

Study Design and Intervention

The intervention suggested in this study will be based off of Stephen et al. (2016). Their study protocol used a .75units ultrasound guided injection of BT in 4mL of saline into the TFL. The participants were then started on a physical therapy regime, and mean change in knee pain,

measured with the AKPS, and mean change in ITB length, measured with the modified Ober, were measured at 6 weeks[20]. One drawback of this study was the absence of a control group. Therefore, we will be adapting and expanding upon their study design and incorporating the study design outlined in Singer et al. (2011). They employed a placebo control, double-blinded study design where patients were randomized into treatment group and control group. The treatment group received 500units of BT into their VL and the control group received the equivalent volume of saline injected into their VL. Primary outcome at 12 weeks analyzed reduction in knee pain using the AKPS. Treatment crossover was allowed at this point and patients were followed for 24 weeks[14]. From the Singer et al. 2011, we will incorporate the double-blind placebo control methodology, as well as their 24-week end point.

The Noble and Thomas test will not be used as secondary outcome measures, and as neither have been used in previous studies involving BT injections and therefor would be difficult to compare to other relevant literature. In addition, and more importantly, the Noble test is dichotomic and not quantifiable. The test can only be considered positive or negative and has no way to quantifiably measure improvement. While the Thomas test can demonstrate quantifiable improvement, it is considered a more general test of hip flexor flexibility and is not specific to the IT band or TFL[1-3].

Data Collection Techniques

The primary outcome of interest is the reduction in mean knee pain measured by the AKPS. The AKPS is a well-validated assessment tool for self-reported knee pain, and has been used in many of the studies discussed previously to examine the relationship between BT injections and knee pain[14,15,19,20]. Ittenback et al. (2016) conducted a secondary analysis of

prospective epidemiologic data to determine the validity and reliability of the AKPS. The records of 414 teenage females were used for analysis of four different methods of AKPS scoring and analysis. All four scoring formats of the AKPS demonstrated to have a high internal consistency (αcoef = 0.83 to 0.91) (SE: 0.82 to 3.00), and "moderate to high criterion related validity-as determined by physician's diagnosis": 0.92 (13-item form), 0.90 (6-item form)[21].

The modified Ober technique is a physical exam maneuver used to assess tightness of ITB and TFL. This physical exam maneuver is done by having a patient lay on their side, with hips in neutral position, knees straight, and with the leg of interest on top. The provider stands behind the patient, using one hand to stabilize the pelvis and keep the hips in a neutral position, and the other to abduct and extend the superior leg with knee at 0°, and then slowly allows the leg to adduct to its resting position. In this position, if the leg cannot fully adduct and remains above the lower knee the test is considered positive and a sign in ITB/TFL tightness[1,20,22]. Reese and Brandy (2003) used an inclinometer to measure the degree of hip adduction or abduction of the leg in the Ober and modified Ober position in a study of sixty-one subjects. A horizontal leg was considered to be at 0°, adduction was recorded as a positive number, and abduction was recorded as a negative number. This study demonstrated the interclass correlation values for the reliability modified Ober test was 0.91, illustrating the modified Ober test is reliable assessment of ITB/TFL flexibility[22]. This method was also used in a study discussed previously by Stephen et al. (2016) to assess the relationship between BT injections into the TFL and ITB length.

Data Analysis

For calculating effect and sample size we will be using the study framework and results from Stephen et al. (2016) and Singer et al. (2011) as they are studies of similar populations

looking for mean change in knee pain using the AKPS as their primary outcome. Stephen et al. (2016) based their power calculation off changes in AKPS in a similar population studies in Singer et al. (2011), demonstrating that they needed a sample size of 45 to calculate an 80% power 95% confidence. To account for drop out 55 patients were recruited, and 45 patients completed the study. They used paired T-tests were used to compare pre-injection AKPS scores to endpoint AKPS scores[20]. In contrast, in Singer et al. (2011) they used unpaired T-tests to compare changes in AKPS scores between treatment and control group. The study being proposed will use a combination of the data analysis outlined in Stephen et al. (2016), using paired T-tests to monitor for changes in AKPS and modified Ober tests within groups, and Singer et al. (2011), using unpaired T-tests to illustrate mean changes in AKPS and modified Ober tests between groups. As these two studies are most prominent in the medical literature, and most similar to our outcome of interest, our study design will incorporate aspects of their design to allow for consistent data across studies that can be readily comparable.

Safety and Monitoring of Adverse Events

Very few serious adverse effects have been noted in previous studies that used BT injections into the VL for knee pain. Stephen et al. 2016 noted two mild adverse events: one patient experienced increased pain after injection, and one patient had an anxiety attack the day after the injection, which the patient felt could have been related to the injection. The only adverse event in Singer et al. (2006) was injection site pain and soreness. Singer et al. (2011) noted injection site bruising and soreness and slight distal thigh asymmetry as an adverse event in their study. Finally, in Chen et al. (2015), no adverse events were reported. These studies

demonstrate that the intervention being proposed is relatively safe and low risk; the study design will reflect the risk level appropriately while being vigilant for any possible complications.

Review of Confounding Variables

There are a few confounding variables, worthy of note, and present in this study including physical therapy adherence, variability in outcome measures, and demographic variance. While study design will attempt to control for these and minimize their effects on study outcome, it is important that they be acknowledged.

Physical Therapy Adherence

It is well known that physical therapy is considered first line standard of care for ITBS, and in itself generally produces a reduction in patient's pain level[23,24]. Therefore, it is safe to assume that the more adherent a patient is to the physical therapy regime in this study, the more likely they are to have a reduction in knee pain regardless of intervention status. Results can also be impacted by the variability in instruction provided by physical therapist, and how much the physical therapy program must be tailored to patient's needs. These variables will be controlled for as best as possible in study design, but it is important to be cognizant of the relationship between physical therapy and reduction in ITBS symptoms.

Variability in Outcome Measurements

The primary outcome of interest is the mean reduction in knee pain between the treatment and the control group measured with the AKPS. The AKPS has been demonstrated to be a valid measurement tool for self-reported symptoms, and is widely used in the orthopedic community[21]. While this assessment tool has demonstrated a high degree of reliability, it is important to note that it is still a patient self-report of pain and therefore is inherently subjective. The secondary outcome of interest, mean change in IT band length, measured with the modified Ober test, demonstrates a slight variability in outcome measurements, as it is a modified physical exam technique and therefore operator dependent. Although it has been demonstrated to be a reliable technique to measure ITB/TFL length and has been used as a method of data collection in previous studies[20,22], it must still be acknowledged that this measurement is user dependent and therefore comes with variability.

Demographic Differences

It has been well documented in epidemiology statistics that women have higher rates of ITBS than men[1,3,25,26]. In Day and Gillet (2019) 30 asymptomatic patients (15 male, 15 female) ran while data were collected via motion-capture system and force platform. Females demonstrated a statistically significant higher ITB strain rate than in men ($p<0.05$)[25]. In an observational cross-sectional study by Kim et al. (2019), authors measured ITB strain using real time elastography ultrasound and found an increased IT band strain with genu varum knee alignment when compared to normal women (4.42 ± 1.42, $P = .048$) and normal men (3.50 ± 1.04, $P = .005$)[26]. It has been suggested that it is a difference in biomechanics and hip muscle activation that may account for this prevalence difference between sexes[1,4,25,26]. This

demographic difference may contribute to a selection bias and influence data outcomes based upon the ratio of male to female participants.

Conclusion

The exhaustive search of the medical literature presented demonstrates an ample amount of evidence in favor of the hypothesis and study design being proposed. Through the research presented above, we can see that ITBS is often associated with weak hip abductors by over activation of the TFL, leading to tightness and inflammation of the ITB; which is why hip strengthening physical therapy and lengthening of the ITB provide symptom relief[1,2,4,5]. It has also been demonstrated the BT injections have shown successful outcomes in the treatment of knee pain when injected into the VL for patellofemoral syndrome[13-16] and into the TFL for superolateral fat pad impingement and ITBS[20]. The review of the literature supports this study's proposed mechanism of action, that temporary paralysis of the TFL will allow for more effective hip abductor strengthening and ITB lengthening, resulting in a significant reduction in knee pain.

Chapter 2 Citations

1. Baker RL, Fredericson M. Iliotibial Band Syndrome in Runners: Biomechanical Implications and Exercise Interventions. *Phys Med Rehabil Clin N Am.* 2016;27(1):53-77.

2. Kirk KL, Kuklo T, Klemme W. Iliotibial band friction syndrome. *Orthopedics.* 2000;23(11):1209-1214; discussion 1214-1205; quiz 1216-1207.

3. Messier SP, Edwards DG, Martin DF, et al. Etiology of iliotibial band friction syndrome in distance runners. *Med Sci Sports Exerc.* 1995;27(7):951-960.

4. Fredericson M, Cookingham CL, Chaudhari AM, Dowdell BC, Oestreicher N, Sahrmann SA. Hip abductor weakness in distance runners with iliotibial band syndrome. *Clin J Sport Med.* 2000;10(3):169-175.

5. Baker RL, Souza RB, Rauh MJ, Fredericson M, Rosenthal MD. Differences in Knee and Hip Adduction and Hip Muscle Activation in Runners With and Without Iliotibial Band Syndrome. *Pm r.* 2018;10(10):1032-1039.

6. Akyuz Unsal AI, Ozkan SB, Ziylan S. Role of Botulinum Toxin Type A in Cyclic Esotropia: A Long-Term Follow-up. *J Pediatr Ophthalmol Strabismus.* 2019;56(6):360-364.

7. Lee SA, Choi JY, Oh BM. The Effect of Computed Tomography-Guided Botulinum Toxin Injection on Cervical Dystonia, Confirmed by a 9-Month Follow-Up Using Positron Emission Tomography/Computed Tomography. *Am J Phys Med Rehabil.* 2020;99(1):e7-e10.

8. Tater P, Pandey S. Botulinum toxin in movement disorders. *Neurol India.* 2018;66(Supplement):S79-s89.

9. Vastik M, Hok P, Hlustik P, Otruba P, Tudos Z, Kanovsky P. Botulinum toxin treatment of freezing of gait in Parkinson's disease patients as reflected in functional magnetic resonance imaging of leg movement. *Neuro Endocrinol Lett.* 2016;37(2):147-153.

10. Brunner R, Krauspe R, Romkes J. [Torsion deformities in the lower extremities in patients with infantile cerebral palsy: pathogenesis and therapy]. *Orthopade*. 2000;29(9):808-813.

11. Kunju P, Ismail R, Sreedharan M, Iype M. Role of botulinum toxin A in cerebral palsy–15 Yrs experience. *Journal of the Neurological Sciences.* 2019;405:98.

12. Dunne JW, Singer BJ, Silbert PL, Singer KP. Prolonged vastus lateralis denervation after botulinum toxin type A injection. *Mov Disord.* 2010;25(3):397-401.

13. Singer BJ, Silbert PL, Dunne JW, Song S, Singer KP. An open label pilot investigation of the efficacy of Botulinum toxin type A [Dysport] injection in the rehabilitation of chronic anterior knee pain. *Disabil Rehabil.* 2006;28(11):707-713.

14. Singer BJ, Silbert PL, Song S, Dunne JW, Singer KP. Treatment of refractory anterior knee pain using botulinum toxin type A (Dysport) injection to the distal vastus lateralis muscle: a randomised placebo controlled crossover trial. *Br J Sports Med.* 2011;45(8):640-645.

15. Silbert BI, Singer BJ, Silbert PL, Gibbons JT, Singer KP. Enduring efficacy of Botulinum toxin type A injection for refractory anterior knee pain. *Disabil Rehabil.* 2012;34(1):62-68.

16. Chen JT, Tang AC, Lin SC, Tang SF. Anterior knee pain caused by patellofemoral pain syndrome can be relieved by Botulinum toxin type A injection. *Clin Neurol Neurosurg.* 2015;129 Suppl 1:S27-29.

17. Cullen DM, Boyle JJ, Silbert PL, Singer BJ, Singer KP. Botulinum toxin injection to facilitate rehabilitation of muscle imbalance syndromes in sports medicine. *Disabil Rehabil.* 2007;29(23):1832-1839.

18. Drake DF, Pidcoe PE, Ericksen J. Botulinum toxin type A for nonsurgical lateral release in patellofemoral pain syndrome: a case study. *Mil Med.* 2011;176(6):696-698.

19. Singer BJ, Silbert BI, Silbert PL, Singer KP. The Role of Botulinum Toxin Type A in the Clinical Management of Refractory Anterior Knee Pain. *Toxins (Basel).* 2015;7(9):3388-3404.

20. Stephen JM, Urquhart DW, van Arkel RJ, et al. The Use of Sonographically Guided Botulinum Toxin Type A (Dysport) Injections Into the Tensor Fasciae Latae for the Treatment of Lateral Patellofemoral Overload Syndrome. *Am J Sports Med.* 2016;44(5):1195-1202.

21. Ittenbach RF, Huang G, Barber Foss KD, Hewett TE, Myer GD. Reliability and Validity of the Anterior Knee Pain Scale: Applications for Use as an Epidemiologic Screener. *PLoS One.* 2016;11(7):e0159204.

22. Reese NB, Bandy WD. Use of an inclinometer to measure flexibility of the iliotibial band using the Ober test and the modified Ober test: differences in magnitude and reliability of measurements. *J Orthop Sports Phys Ther.* 2003;33(6):326-330.

23. Beals C, Flanigan D. A Review of Treatments for Iliotibial Band Syndrome in the Athletic Population. *J Sports Med (Hindawi Publ Corp).* 2013;2013:367169.

24. Strauss EJ, Kim S, Calcei JG, Park D. Iliotibial band syndrome: evaluation and management. *J Am Acad Orthop Surg.* 2011;19(12):728-736.

25. Day EM, Gillette JC. Acute Effects of Wedge Orthoses and Sex on Iliotibial Band Strain During Overground Running in Nonfatiguing Conditions. *J Orthop Sports Phys Ther.* 2019;49(10):743-750.

26. Kim DY, Miyakawa S, Fukuda T, Takemura M. Sex Differences in Iliotibial Band Strain under Different Knee Alignments. *Pm r.* 2019.

Chapter 3 – Study Methods

Study Design

The study being proposed will be a double-blinded, placebo-controlled, randomized control trial, to investigate the use of botulinum toxin type A injection into the tensor fasciae latae as a viable adjunct treatment for chronic refractory ITBS.

Study Population and Sampling

Patients, ages 18-50, will be recruited from orthopedic sports medicine clinics that have a history of chronic or refractory ITBS. Patients with ITBS will be selected on history, and physical exam. X-ray and MRI may be used to rule out any other structural pathology if already available in a patient's history.

Patients were considered if they met the following inclusion criteria:

1. Symptoms lasting longer than 6 months
2. History of previously failed physical therapy, for at least two months
3. Pain localized to the anterolateral knee
4. Pain worsens with strenuous athletic activity.

Patients were excluded from the study if they met any of the following exclusion criteria:

1. Previous surgery on injured knee
2. Knee instability
3. Current injury to the knee other than to the IT band (ex: patellar subluxation, tendon t ear, or fracture)
4. Moderate or severe osteoarthritis

Subject Protection and Confidentiality

Study design will be submitted to Yale's Institutional Review Board for approval through the IRES IRB system. Patient consent forms will ensure that patient's data will not be shared without their consent. Forms will state that we will not share patient data or information with outside parties, and all data published or shared will be deidentified. Consent will allow researchers full access to the patients' medical records for study research as well as patient safety. All members of the research and treatment teams will sign confidentiality and HIPPA agreements.

Recruitment

Patients will be recruited from orthopedic sports medicine and primary care sports medicine clinics in Connecticut either by provider referral, review of medical record, or patient request. Recruitment flyers will also be posted at athletic facilities, physical therapy practices, and orthopedic clinics throughout the greater New Haven area. All patients will undergo a thorough review of their medical records, as well as history and physical examination by the study's lead providers to confirm patients' eligibility.

Study Variables and Measures

The independent variable, which will be received by the treatment gorup, is the injection of .75 units of botulinum toxin type A (BT) in 4mL of saline into the TFL. The control group

will not receive the independent variable and will instead receive a placebo injection of 4mL saline into their TFL. Both the treatment group and the control group will receive the same physical therapy instruction.

The main dependent variable, and primary outcome, is mean reduction in pain from baseline measured via the AKPS at 24 weeks. The AKPS is a self-reported knee pain scale that provides a more detailed look at knee pain in relation to patient activity and functional level. The AKPS will be administered at week 0, 1, 2, 4, 8, 12, and 24 to monitor the effects of treatment overtime. The primary outcome of interest in mean reduction in knee pain, measured with the AKPS, from week 0 to week 24.

The secondary outcome of interest will be the mean change in IT band length from baseline. IT band length will be measured using the modified Ober test, where flexibility will be measured with an inclinometer. The modified Ober test is a physical exam maneuver where the patient lies on their unaffected side while the provider extends their injured leg with the knee in extension. The inclinometer is then placed on the lateral epicondyle of the femur. Abduction is read as a negative number, adduction read as a positive number, with true horizontal reading at 0°. IT band length will be measured at baseline, and at 1, 2, 4, 8, 12, and 24 weeks.

Physical Therapy Regime Received by Both Groups

Physical therapy for both groups will follow standard practice guidelines for ITBS and will primarily consist of diffuse, lower-extremity stretching focused on the IT band, hamstring, gastrocnemius, and soleus. In addition, physical therapy will also include strengthening components focused on the hip abductors and quadriceps. Physical therapy will be conducted once a week by certified physical therapists at Yale Physical Therapy Centers in New Haven and

Milford. Physical therapy sites will be trained on study protocol and the specific rehab regiment. These physical therapists will be instructed to perform the same set of exercises with all patients, educate the them about at home exercises, and advance the them as appropriate.

Patients will all be given a physical therapy exercise log that outlines the week's exercises. They will meet with the physical therapist on the first day of each new exercise log week so the physical therapist can instruct them on proper exercise technique. Every patient will be given the same set of exercises each week. The exercise difficulty will increase each week. At any point throughout the study, if the patient cannot tolerate the increase in difficulty or if the physical therapist recommends not advancing the patient, they will continue to repeat the highest level of difficulty tolerated until they can progress further, or the study ends.

Blinding of Intervention

To ensure continuity in technique and limit bias, the same provider will perform all injections. This provider will be the only unblinded member of the research team, and after administration of injection will not participate in further patient care, data gathering, or data analysis. The patient, physical therapist, and continuing care provider will be blinded to which treatment the patient has received.

Assignment of Intervention

Patients will be randomized into two groups of roughly 150 participants, depending upon recruitment, via computer generator stratification program. These randomized control and intervention groups will be subsequently stratified based on age, gender, weight, activity level,

IT band length relative to height, and baseline pain score. Random treatment allocation and variable stratification will help ensure that the two groups are as uniform and comparable as possible.

Adherence

The initial intervention, which is the independent variable, is a one-time injection into the TFL. This is done under direct supervision of research staff and therefore adherence to the intervention will not be an issue in this study. However, the physical therapy adherence and activity level compliance need to be monitored. The physical therapists will fill out a patient adherence form that will include: how many treatment sessions were missed and a qualitative assessment of patient adherence and progression in physical therapy activities. Patients will receive a physical therapy log that outlines each day's physical therapy activities and with a box to check when completed. The patients will update this log each day to mark their completion of that day's activities. At the end of each week's physical therapy log they will be asked to sign to attest to their log's accuracy. This log will be shared with the research staff at each office visit to track patient's adherence to physical therapy regiment.

Monitoring of Adverse Events

No significant adverse effects were noted in any previous study of BT injections into the TFL or the VL. Mild adverse effects that did occur were injection sight pain, redness, and one anxiety attack. For these mild, but possible, adverse events we will have patients fill out a self-reported questionnaire throughout the study. Questionnaires on adverse events will be performed

on the day of injection, and at each research visit. Patients will be encouraged to reach out to the researchers at any point in the study with whatever concern they may have. The only severe adverse events that are notable are infection or allergic reaction from the injection. Although, we consider this to be very unlikely and has not been seen as an outcome in any previous studies of note. For this and any other severe adverse event, we will encourage patients to seek medical attention promptly, document the adverse event thoroughly, and release them from the study.

Data Collection

The primary outcome of interest is mean reduction in knee pain from baseline. This will be measured using the AKPS and will be assessed at research office visits at week 0, 1, 2, 4, 8, 12, and 24. The secondary outcome of interest is the mean change in IT band length from baseline. IT band length will be assessed through the modified Ober test and measured with an inclinometer at week 0, 1, 2, 4, 8, 12, and 24. Both of these data collection techniques are outlined in further detail above in "Study Variables and Measurments." These data points will be collected at baseline and follow up office visits at Yale Physician's Building Orthopedic Clinic by study provider.

Sample Size Calculation

For the given effect size (population means of 15.00 vs. 8.60), standard deviation of 16, treatment group sizes of 148 and 148, and an alpha of 0.010 for a 2-tailed T-test the power is 0.801. A Bonferoni correction was chosen correcting our alpha to 1% to correct for errors in sample size calculations and prevent a false positive. For this study we will need a sample size of

296 to discern a significant difference between treatment and placebo group analyzed with a 2-tailed T-test. To account for an expected 10% attrition rate 330 patients will need to be enrolled. Sample size calculations are based on results from Singer et al. 2011 and Stephen et al. 2016.

Analysis

Both the primary outcome of interest, reduction in knee pain from baseline, and the secondary outcome, change in IT band length from baseline, will be treated as continuous variables. These variables will be compared individually by the students paired T-test, and as a mean change by group with the student T-test. The random allocation of control and treatment groups in combination with group stratification based on possible confounding variables will allow for easily comparable homogenous groups.

Timeline and Resources

The Recruitment Phase is the first phase of the study that will run for one year from 01/01/2021-12/31/2021. The Experimental Phase will overlap with the recruitment phase by six months and will also last one year from 07/01/2021- 06/31/2022. With the last patients will be enrolled in the study at the end of 2021, and the study run for 6 months, the latest patients enrolled will be finished with the study protocol by mid 2022. Data will be collected throughout the experimental phase. This will leave six months for the final analysis phase, from 07/01/2022-12/23/2022, where final data collected in the experimental phase will be analyzed and disseminated.

The study will be conducted at Yale Orthopedics/Sports Medicine at the Yale Physicians Building in New Haven, CT. The research team will include four providers. The first provider will be the only unblinded member of the study. This unblinded member will administer the injection into the TFL and will not be involved in any other aspect of research after injection administration. The other three providers will assist with recruitment, perform baseline assessment and confirm diagnosis of chronic ITBS. They will also conduct the study's follow-up visits and perform the modified Ober test to measure IT band length. Physical therapists from different Yale physical therapy sites throughout the greater New Haven area will be needed to conduct physical therapy sessions with participants. Finally, a team of five research assistants will be needed to help with patient recruitment, enrollment, data collection and analysis. Besides botulinum toxin injections, equipment already available at the sports medicine clinic and physical therapy offices will be sufficient for study needs.

Ethical Considerations

While this study proposes a relatively safe and non-invasive procedure, there are a few ethical considerations to be addressed including randomized allotment of treatment and control groups. Both groups will receive injections, which carry their own risks of infection, injection site pain, bruising, and swelling. The placebo group will receive an injection without the possibility of treatment. While the treatment group will receive an off-label use injection. Both groups carry their own risks and ethical considerations, which will be carefully monitored throughout the study. Overall the study proposed is a relatively safe procedure with minimal risk and ethical concerns.

Chapter 4 – Conclusion

Advantages and Disadvantages

Problem Definition

The problem, as stated, is a lack of treatment options for patients with chronic ITBS who fail conservative management. This is particularly common in highly active and athletic patients, not only because ITBS is more prevalent in these populations, but also because these patients often have a hard time refraining from activity long term. In an overuse injury such as ITBS, pain is provoked with increased activity. For those who fail traditional rest and physical therapy techniques their options are either to maintain their activity level and experience pain, undergo surgical intervention, or forever limit their activity and athletics. The goal of this study was to propose a new intervention that would allow patients to reduce their pain levels and avoid surgery, while maintaining their activity level and quality of life.

As athletes and active adults often have the highest rates of ITBS, because of this our study population will have high rates of athletes and atcive adults than represented in the general public. This makes the results less applicable to the general population. In addition, as ITBS is a syndrome of overuse, this population with the highest level of activity will presumably have the most severe symptoms at baseline. With a higher starting point for symptom severity, it will be easier to find a statistically significant reduction in symptoms. While this is not likely to cause a significant problem in data analysis, it is important to keep in mind the applications of this study in reference to the study population.

Validity of Methods

The methods outlined in this study represent the most rigorous and detailed approach possible within practical limits. The study design is a randomized, double-blind, placebo-control trial, chosen to yield the highest level of empirical results. Treatment group allocation is done randomly and then stratified based on demographics and possible confounding variables to ensure the most homogenous groups possible for comparison. Allocating treatment allows for the intervention effect to be examined more precisely, by reducing allocation and selection bias. Patients, providers, physical therapists, and researchers were blinded to treatment allocation, reducing both the placebo effect and experimenter bias.

The primary outcome of interest, mean reduction in anterior knee pain at 6 months, was measured with the AKPS. The drawback to using the AKPS as a tool in a placebo trial is that patients not receiving the intervention might believe that they are and therefore experience a placebo effect reduction in pain. However, patients in the intervention group that might experience the same phenomena should match this effect. Since the AKPS is solely self-reported with no additional empiric data, it comes with its own limitations. While the AKPS is inherently subjective as it is a self-reported pain scale, it has been demonstrated to be a valid measurement for anterior knee pain. The AKPS is also one of the more popular surveying tools used in orthopedics, and was used in multiple previous studies, making our results easily comparable to the relevant medical literature.

The secondary outcome of interest, mean change in ITB length, measured with the modified Ober test allowed for understanding of the physiology behind ITBS. A correlation between increased ITB length and reduction of pain suggests a relationship between ITBS knee pain and ITB length. This however is not enough to demonstrate causation, but in combination

with the medical literature, supports the theory that ITBS associated knee pain is due in part to a short and tight ITB. Furthermore, this correlation suggests a mechanism for why BT injections into the TFL could reduce ITBS related knee pain. By paralyzing the TFL the ITB is allowed to relax and lengthen, leading to a reduction of inflammation and pain.

In terms of analyzing our primary and secondary outcome data, both the paired T-test and unpaired T-test were utilized. The paired T-test allowed for comparison of individual data, comparing each participant's baseline to their endpoint to determine if they had experienced a significant change in knee pain or IT band length. This helped us further explore the relationship between ITB length and knee pain in patients with chronic ITBS. In addition, it also helped us look at individual responses to either the intervention or control and break down results based on demographic and confounding variables for a more in-depth statistical analysis.

The unpaired T-test was utilized to understand the mean change difference in outcome variables between groups. The mean change in knee pain and ITB length was calculated for each group and compared with the unpaired T-test to determine if there was a statistically significant difference in outcome between the two groups. The unpaired T-test comparing the mean reduction in knee pain between the control and treatment groups was considered the primary outcome of interest in this study. Therefore, this test determines the validity of the study's hypothesis, and whether we can view BT injections into the TFL as a viable adjunct treatment for chronic ITBS.

Both the paired and unpaired T-tests are highly validated techniques used to determine if a difference between two groups is significant. The only drawback in their utilization is the limit in their ability, they cannot track changes over time, analyze time to an event, or determine the number needed to treat. These outcomes were not addressed in our analysis as they were not a

part of this study's hypothesis and not accounted for is the study design. For our purposes the T-tests are sufficient to determine the validity of our hypothesis.

Generalizability of Study Results

The results of this study hold great significance for patients suffering with chronic ITBS as it offers a viable adjunct treatment for their pain, avoid surgical intervention, and return to their level of activity/athletics without issue. The patient population in this study was 18-55 with chronic ITBS. As ITBS is a syndrome of overuse our study population will primarily consist of athletes and active adults by default. Therefore, the results of this study are easily applied to populations such as college athletes, military recruits, and generally active or athletics adults with chronic ITBS. As the study population was composed of chronic ITBS patients, and because physical therapy is known to be a successful initial treatment for ITBS, the results of this study are not necessarily applicable to all patients with ITBS. In addition, this study did not look at populations outside the 18-55 age range, populations with additional knee complications, or sedentary populations with ITBS. Therefore, the results of this study cannot be applied directly to these populations but can serve as a guide for future studies and treatment interventions in these groups.

Although the results of this study may not be applicable to all patients with ITBS, it does have further applications outside of the ITBS patient populations. Research in other muscular imbalance syndromes with similar pathophysiology to ITBS, in particular patella femoral syndrome, could benefit from the results of this study. While the results of this study may not be specifically generalizable to outside of ITBS, they are relevant to a wide variety of similar conditions. In addition, the results of this study give us more information about the safety and efficacy of BT treatment and may open the door for its use in other conditions.

Clinical Significance

Successful use of BT to treat ITBS would leave a positive impact on clinical practice and ITBS treatment. Successful implementation of this strategy could reduce the number of patients opting for surgical intervention. Surgery comes with a greater risk of complications and a greater expense to the patient. Avoiding surgery would allow for an overall reduction in both risk and cost for the patient. BT treatment being less expensive than surgery would also offer a treatment option for patients with chronic ITBS that could not afford surgery, creating a treatment option that is more accessible to a wider population. With the possibility of more patients with chronic ITBS opting for BT intervention due to its minimal risk and cost, we could see a greater reduction in prevalence of chronic ITBS.

BT therapy for ITBS not only allows for a viable alternative treatment for ITBS itself but creates an avenue for new therapies and greater understanding of various pathologies. Successful use of BT here would provide a basis for BT therapy in other disorders related to the IT band, including greater trochantic bursitis, and to other muscle imbalance disorders. In addition to promising therapeutic discoveries, this study will also afford researchers a greater understanding of the pathology behind ITBS. As the IT band is connected in some way to almost all the major components of the lower limb, a deeper understanding of its biomechanics is crucial to a wide variety of pathologies. By inhibiting one of the IT band's major muscle attachments we can gain a greater understanding of its biomechanics that could lead to more affective physical therapy and other treatments.

Finally, BT treatment for ITBS is a less risky and medically intensive procedure, allowing for mid-level providers such as PAs and NPs to perform this without needing physician

supervision. Many PAs across the country, and in a wide variety of medical specialties already treat and care for patients with ITBS. This treatment strategy, if proven a viable adjunct therapy for ITBS, could commonly be performed in outpatient orthopedic, sports medicine, and even primary care clinics. BT treatment will give patients and providers a greater array of noninvasive treatment options for refractory and chronic ITBS, leading to more autonomous treatment options for ITBS by PAs.

APPENDIX A: Sample HIC

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Tensor Fasciae Latae Botulinum Injections as an Adjunct Treatment for Iliotibial Band Syndrome

Principal Investigator: Michael Medvecky, MD; J. Morgan Jones, PA-SII

Funding Source: Yale University School of Medicine: Physician Associate Program

Invitation to Participate and Description of Study

You have been invited to participate in a study to test the effects of botulinum toxin (Botox) injections into the tensor fasciae latae on chronic iliotibial band syndrome related knee pain. You have been asked to participate because you have been diagnosed with iliotibial band syndrome, have previously failed conservative therapy, and have had symptoms for more than six months. Approximately 300 patients will participate in this study.

Iliotibial band syndrome is a common injury of overuse seen in athletes and active populations. It is categorized by inflammation of the iliotibial band causing irritation and knee pain. The standard of care for this condition is considered to be conservative management of rest and physical therapy. However, many patients fail conservative therapy and develop chronic symptoms. For these patients the next level of management is considered to be steroid therapy and/or surgical release of the iliotibial band. Both of these second line therapies come with their own increased set of risks.

This study proposes an alternate adjunct therapy for patients with chronic iliotibial band syndrome with the hopes of symptom reduction and to prevent the need to escalate to steroid/surgical therapies. Thus, producing a viable alternative therapy to improve patient's symptoms and quality of life while allowing them to avoid more invasive and expensive therapeutic options.

In order to decide if you wish to participate in this study, it is important to understand the study's procedure and all risks associated with it. This form provides information about study protocol as well as risk and benefits. A research team member will review this form with you and make sure you understand what will be expected of you, outline the procedure, explain all the risks involved, and answer any questions you may have. Once you understand the study you will be asked if you wish to participate, if so you will be asked to sign this form.

Description of Procedures

This study's purpose is to investigate the efficacy of using botulinum toxin injections into the tensor fasciae latae in combination with physical therapy to improve iliotibial band syndrome associated knee pain. Roughly 330 patients will be enrolled and then randomized into either the treatment group or the control group. Randomization will be done via computer generator and will not be based on any personal data. Neither the patient nor the research team will know what treatment group you have been assigned to. Patients randomized to the treatment group will receive a one-time injection of .75units of botulinum toxin into their tensor fasciae latae. Patients randomized to the placebo group will receive a one-time injection of 4mL of saline into their tensor fasciae latae. Both groups will be given the same physical therapy regime. The length of the study from injection to conclusion is 24 weeks.

Participants will be expected to participate in eight total office visits. At each office visit we will ask participants to fill out the Anterior Knee Pain Scale (AKPS) to monitor their symptoms severity. In addition at every visit the research provider will perform a physical exam maneuver called the modified ober test, where the participant lays on their side and the flexibility of their IT band is measured with an inclinometer. An inclinometer is a noninvasive instrument placed against the leg of the patient that reads the angle at which the leg is resting.

Visit 1- Pre-Study: Study eligibility evaluation and consent, AKPS and Modified Ober Test.

Visit 2- Week 0: Tensor fasciae latae injection, AKPS and Modified Ober Test.

Visit 3- Week 1: Check up with research staff, AKPS and Modified Ober Test.

Visit 4- Week 2: Check up with research staff, AKPS and Modified Ober Test.

Visit 5- Week 4: Check up with research staff, AKPS and Modified Ober Test.

Visit 6- Week 8: Check up with research staff, AKPS and Modified Ober Test.

Visit 7- Week 12: Check up with research staff, AKPS and Modified Ober Test.

Visit 8- Week 24: Study Conclusion. Check up with research staff, AKPS and Modified Ober Test.

In addition to office visits patients will be required to attend physical therapy once a week, and conduct at home exercises once a day. Patients will keep track of their at home physical therapy through a physical therapy log that will be reviewed by the research team at appointments to track therapy progress and adherence. Aside from physical therapy patients are encouraged to rest, and advance to more strenuous activity as advised by the physical therapist.

All study participants will be kept informed of any major study developments as they occur. If for any reason we find that one treatment is superior to the other during the course of the study, we will terminate the study and offer the superior treatment to all participants. Participants are encouraged to reach out to research staff if they have questions, concerns, or issues at any point in the trial. Patients will be able to withdraw from the study at any point with no penalty or consequences.

This study and all relevant information will be listed on clinicaltrials.gov in accordance with national law. You are welcome to access information on this study at this site at any time.

Risks and Inconveniences

We do not anticipate any significant risks or adverse events while participating in this study. The most likely adverse event will be injection site pain or bruising, this will be monitored for and the study will provide ice packs and NSAIDs on day of injection at patients request on injection day to offset this inconvenience. An unlikely but possible risk of this procedure in injection site infection, injections will be done with proper sterile technique to minimize this risk. Theoretical side effects include allergic reaction, muscle atrophy, and tendon rupture. These are all highly unlikely and are only theoretical risk as both botulinum toxin and saline have been demonstrated safe drugs and none of these adverse events have been reported in similar previous studies.

Benefits

Patients will be offered standard of care physical therapy free of charge during their participation, which has been demonstrated to improve ITBS symptoms. In addition the

implementation of botulinum toxin may significantly decrease ITBS symptom severity and improve physical therapy outcomes.

Economic Considerations

Patients will not be offered compensation for study participation.

Treatment Alternatives

There are no study alternatives. If you do not wish to participate in the study you may wish to pursue treatment from another provider or continue conservative treatments on your own.

Confidentiality and Privacy

All identifiable data obtained throughout the course of this study will remain confidential and will only be released with your permission or in accordance with state or federal law. When the results of this study are published, presented, or shared all data will be deidentified meaning no information would be related to you or reveal your identity unless permission is granted by you to do so. Only in cases of abuse to yourself or another, intent to harm yourself or another, or with certain reportable diseases would your information be mandated by law to be shared with proper authorities.

By signing this form and enrolling in this study you will allow this research committee to have access to your medical records including past doctors notes and previous imaging. This is done to ensure your safety in this study and to ensure you are an eligible candidate. The information from your medical history will not be shared with any outside party or published. The research team will deidentify all identifiable data, such as your name or birthdate, and will code your identity before any data from the study is shared. We will only collect data and

information relevant to the study protocol and your safety. The data will be stored and collected on an encrypted HIPPA compliant server.

The Yale Human Research Protection Program and the Yale Human Investigation Committee will have access to your personal information during the course of the study to ensure research compliance and participant safety. These individuals are required to maintain confidentiality.

Voluntary Participation Withdrawal

Participation in this study is completely voluntary and you may withdraw at any time. You are free to choose to decline this study. Declining this study will not bar you from receiving medical care that you are entitled to, and will not restrict you from seeking care in any way. However refusing to participate in this study means you will not receive possible beneficial treatments.

Withdrawing from the Study

If you do choose to enroll in this study, you are free to stop at any time. There will be no penalty or consequence of stopping the study. If you start the study and wish to stop, please simply contact a research team member by phone or email to let us know you no longer wish to participate. Once you withdraw your permission no new data will be collected. Data already collected will remain deidentified and will be used throughout the course of the study to maintain study integrity.

Questions

Please let us know if there is anything, medical or legal, that you did not understand or was not explained properly in this form. Our research staff is happy to answer all of your questions and ensure you are fully informed before you make the decision to participate or not. Please take the time you need to review this information before making a decision.

Authorization

I have read (or someone has read to me) this form and have decided to continue to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent addendum form.

By signing this form, I give permission to the research team to access my medical record, collect data, and distribute data in accordance with the purposes outlined in this form. By refusing permission, I understand I will not be able to participate in this study.

I willingly consent to participate in the study-specific blinded tensor fasciae latae injection.

Initials: _____ Date:_____

Name of Subject:_____

Signature:_____

Date:_____

_____ _____

Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions, offer input, discuss situations in the event that a member of the research team is not available, or if you have any questions concerning your rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688.

APPENDIX B: Recruitment Flyer

Volunteers Needed for Research Study

Yale University

We are running a study to see if Botox injections can help reduce knee pain from chronic iliotibial band syndrome when combined with physical therapy.

Who is Eligible?

- Ages 18-55
- Patients who have had iliotibial band syndrome for longer than 6 months, and have already failed physical therapy
- Patients who have no other knee conditions or injuries

What will you be asked to do?

- Receive a one time injection into your hip of either saline or Botox
- Participate in once weekly physical therapy sessions and in daily at home physical therapy
- Come to a total of eight office visits over 6 months

If you are interested or have any questions please contact us at:

- **Email: investigator@yale.edu**
- **Phone: (201) XXX-XXX**

APPENDIX C: Sample Size Calculation

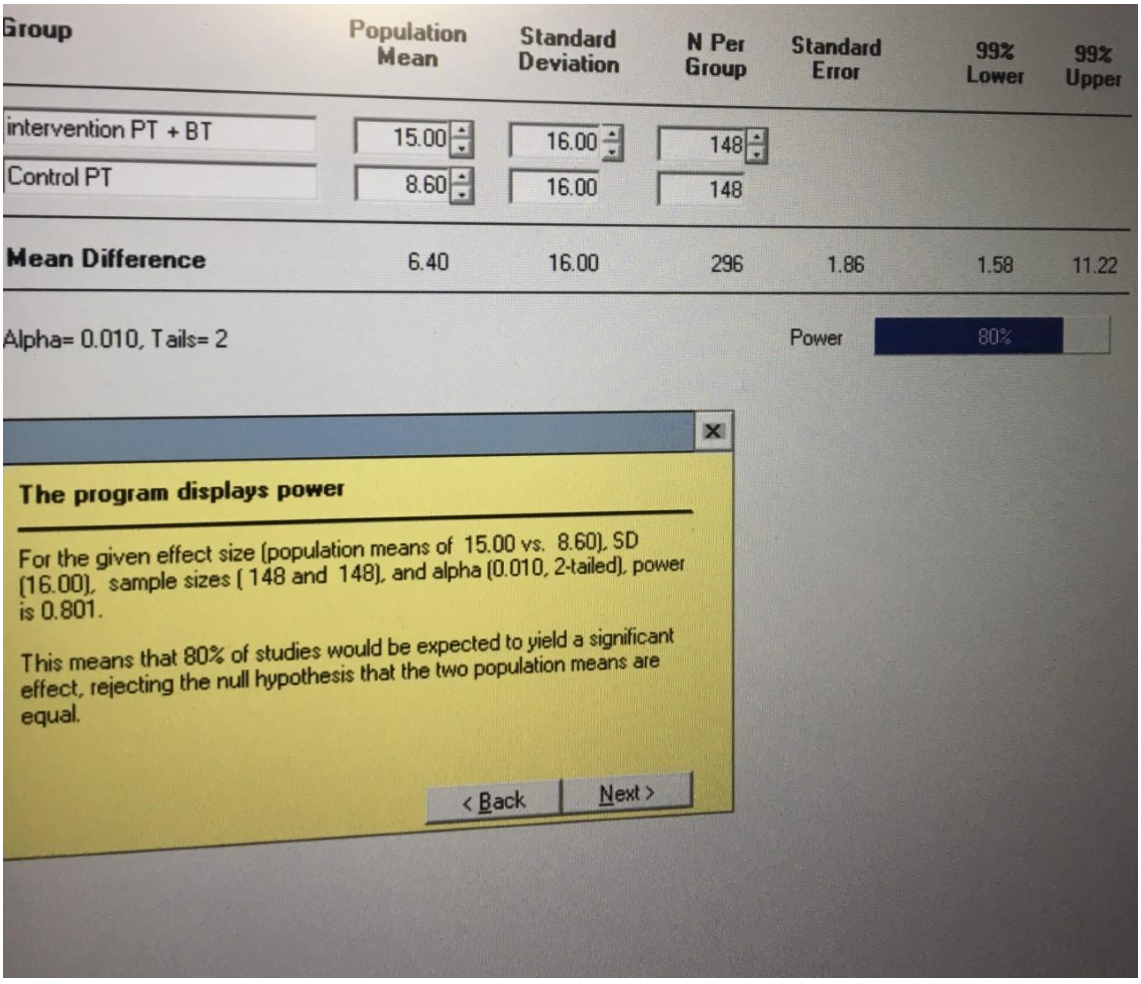
Effect Size was calculated with data from Singer et al. 2011 and Stephen et al. 2016. These numbers were then used to calculate the estimated sample size using Power and Precision 4 Software.

Singer et al. 2011 compared BT injection into the VL to saline injections in the VL coupled with physical therapy for patellofemoral knee pain. In their treatment group they reported mean change in knee pain from baseline using the AKPS in individual categories, reporting a mean change in kneeling 50.5, stair walking 20.9, and squatting 30.8. These numbers were averaged to give a mean AKPS change in the treatment group of 33.6. The placebo group demonstrates a mean change in AKPS from baseline of 20.4. The difference in mean change in AKPS from baseline between the treatment and control group was 13.2. Using this we calculated the retaliate effect to be 57%.

Stephen et al. 2016 examined the effects of BT injections into the TFL with physical therapy for ITBS knee pain, but without a control group. They reported a mean AKPS change of 15 points with treatment. Using the relative effect from Singer et al. 2011 of 57% we calculated an expected effect of an 8.6 point change in the AKPS in the control group. The projected population mean effect of BT + physical therapy in the TFL for ITBS is a 15 point change in the AKPS, while the projected mean effect of Control + physical therapy in the TFL for ITBS to be 8.6.

To increase the likelihood of finding a true statistical significance in our study while reducing sampling error, and Bonferoni correction was done. This alters our alpha from 0.5% to 1%, therefore increasing our sample size. Power and Precision 4 software was used to calculate that with a power of 80%, for a 2-tailed T-test and alpha of 1%, we would need 296 subjects to yield statistical significance and reject the null hypothesis. To account for an expected 10% attrition rate 330 patients will need to be enrolled.

Figure 1. Sample Size Calculation



Calculated using: Power and Precision. Version 4. Biostat, Inc. Englewood, NJ.

APPENDIX D: Sample Physical Therapy Log

ITBS Physical Therapy Log

Dear Participant, this is your exercise log for week one. Your Physical Therapist should review this with you on Day 1, and work through the exercises with you, to make sure you understand the exercises and how to perform them on your own. Please check off the box corresponding to the exercise and date as you preform them. You will return this sheet to the research office at your next appointment and will be given a new exercise log.

Please let the research staff or Physical Therapists know if you have any questions or concerns.

Week 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Standing Legs Criss-cross Arms Overhead 3x30s							
Figure-4 Stretch 3x 30s							
Wall Calf Stretch 3x30s							
Foam Roll Glutes 2x 30s							
Foam Roll Hip Abductors 2x 30s							
Foam Roll IT Band 2x30s							
Clam Shell 2x10							
Side Bridge Hip Dips 2x10							
Extended Crunches 2x10							
Side Lying Hip Abduction 2x15							
Hip Hikes2x10							
Single Leg Step Down 2x10							
Standing Legs Criss-cross Arms Overhead 3x30s							

***All exercises are to be done on both sides, on your injured leg and your non-injured leg

I (participant name) _____ certify that I have completed the exercise regime above to the best of my abilities and have recorded my progress accurately.

Participant Signature _____
Date_____

APPENDIX E: Anterior Knee Pain (Kujala) Scale

KUJALA SCORING QUESTIONNAIRE

Name: First Last **Date:**

Physician:

1. Limp:
- a) None
- b) Slight or periodic
- c) Constant

2. Support:
- a) Full support without pain
- b) Painful
- c) Weightbearing impossible

3. Walking:
- a) Unlimited
- b) More than 2 km
- c) 1-2 km
- d) Unable

4. Stairs:
- a) No difficulty
- b) Slight pain when descending
- c) Pain both when ascending and descending
- d) Unable

5. Squatting:
- a) No difficulty
- b) Repeated squatting painful
- c) Painful each time
- d) Possible with partial weightbearing
- e) Unable

6. Running:
- a) No difficulty
- b) Pain after more than 2 km
- c) Slight pain from the start
- d) Severe pain
- e) Unable

7. Jumping:
- a) No difficulty
- b) Slight difficulty
- c) Constant pain
- d) Unable

8. Prolonged sitting with knee flexed:
- a) No difficulty
- b) Pain after exercise
- c) Constant pain
- d) Severe pain
- e) Unable

9. Pain:
- a) None
- b) Slight and occasional
- c) Interferes with sleep
- d) Occasionally severe
- e) Constant and severe

10. Swelling:
- a) None
- b) After severe exertion
- c) After daily activities
- d) Every morning
- e) Constant

11. Abnormal painful kneecap movements:
(patellar subluxations)
- a) None
- b) Occasionally in sports activities
- c) Occasionally in daily activities
- d) At least one dislocation after surgery
- e) More than two dislocations

12. Atrophy of thigh:
- a) None
- b) Slight
- c) Severe

13. Flexion deficiency:
- a) None
- b) Slight
- c) Severe

Score

Appendix Citations

1. Kujala Scoring Questionnaire. (n.d.). Retrieved 2020, from

https://www.hss.edu/secure/files/WSMC-kujala.pdf

Bibliography

Akyuz Unsal AI, Ozkan SB, Ziylan S. Role of Botulinum Toxin Type A in Cyclic Esotropia: A Long-Term Follow-up. *J Pediatr Ophthalmol Strabismus.* 2019;56(6):360-364.

Baker RL, Fredericson M. Iliotibial Band Syndrome in Runners: Biomechanical Implications and Exercise Interventions. *Phys Med Rehabil Clin N Am.* 2016;27(1):53-77.

Baker RL, Souza RB, Rauh MJ, Fredericson M, Rosenthal MD. Differences in Knee and Hip Adduction and Hip Muscle Activation in Runners With and Without Iliotibial Band Syndrome. *Pm r.* 2018;10(10):1032-1039.

Beals C, Flanigan D. A Review of Treatments for Iliotibial Band Syndrome in the Athletic Population. *J Sports Med (Hindawi Publ Corp).* 2013;2013:367169.

Brunner R, Krauspe R, Romkes J. [Torsion deformities in the lower extremities in patients with infantile cerebral palsy: pathogenesis and therapy]. *Orthopade.* 2000;29(9):808-813.

Chen JT, Tang AC, Lin SC, Tang SF. Anterior knee pain caused by patellofemoral pain syndrome can be relieved by Botulinum toxin type A injection. *Clin Neurol Neurosurg.* 2015;129 Suppl 1:S27-29.

Cullen DM, Boyle JJ, Silbert PL, Singer BJ, Singer KP. Botulinum toxin injection to facilitate rehabilitation of muscle imbalance syndromes in sports medicine. *Disabil Rehabil.* 2007;29(23):1832-1839.

Day EM, Gillette JC. Acute Effects of Wedge Orthoses and Sex on Iliotibial Band Strain During Overground Running in Nonfatiguing Conditions. *J Orthop Sports Phys Ther.* 2019;49(10):743-750.

Devan MR, Pescatello LS, Faghri P, Anderson J. A Prospective Study of Overuse Knee Injuries Among Female Athletes With Muscle Imbalances and Structural Abnormalities. *J Athl Train.* 2004;39(3):263-267.

Drake DF, Pidcoe PE, Ericksen J. Botulinum toxin type A for nonsurgical lateral release in patellofemoral pain syndrome: a case study. *Mil Med.* 2011;176(6):696-698.

Dunne JW, Singer BJ, Silbert PL, Singer KP. Prolonged vastus lateralis denervation after botulinum toxin type A injection. *Mov Disord.* 2010;25(3):397-401.

Ekman EF, Pope T, Martin DF, Curl WW. Magnetic Resonance Imaging of Iliotibial Band Syndrome. *The American Journal of Sports Medicine.* 1994;22(6):851-854.

Fredericson M, Cookingham CL, Chaudhari AM, Dowdell BC, Oestreicher N, Sahrmann SA. Hip abductor weakness in distance runners with iliotibial band syndrome. *Clin J Sport Med.* 2000;10(3):169-175.

Holmes JC, Pruitt AL, Whalen NJ. Iliotibial band syndrome in cyclists. *Am J Sports Med.* 1993;21(3):419-424.

Inoue H, Hara K, Arai Y, et al. Outcome of Low-Invasive Local Split-Thickness Lengthening for Iliotibial Band Friction Syndrome. *Int J Sports Med.* 2018;39(3):232-236.

Ittenbach RF, Huang G, Barber Foss KD, Hewett TE, Myer GD. Reliability and Validity of the Anterior Knee Pain Scale: Applications for Use as an Epidemiologic Screener. *PLoS One.* 2016;11(7):e0159204.

Kim DY, Miyakawa S, Fukuda T, Takemura M. Sex Differences in Iliotibial Band Strain under Different Knee Alignments. *Pm r.* 2019.

Kirk KL, Kuklo T, Klemme W. Iliotibial band friction syndrome. *Orthopedics.* 2000;23(11):1209-1214; discussion 1214-1205; quiz 1216-1207.

Kujala Scoring Questionnaire. (n.d.). Retrieved 2020, from https://www.hss.edu/secure/files/WSMC-kujala.pdf

Kunju P, Ismail R, Sreedharan M, Iype M. Role of botulinum toxin A in cerebral palsy–15 Yrs experience. *Journal of the Neurological Sciences.* 2019;405:98.

Lee SA, Choi JY, Oh BM. The Effect of Computed Tomography-Guided Botulinum Toxin Injection on Cervical Dystonia, Confirmed by a 9-Month Follow-Up Using Positron Emission Tomography/Computed Tomography. *Am J Phys Med Rehabil.* 2020;99(1):e7-e10.

Messier SP, Edwards DG, Martin DF, et al. Etiology of iliotibial band friction syndrome in distance runners. *Med Sci Sports Exerc.* 1995;27(7):951-960.

Pegrum J, Self A, Hall N. Iliotibial band syndrome. *Bmj.* 2019;364:l980.

Reese NB, Bandy WD. Use of an inclinometer to measure flexibility of the iliotibial band using the Ober test and the modified Ober test: differences in magnitude and reliability of measurements. *J Orthop Sports Phys Ther.* 2003;33(6):326-330.

Rumball JS, Lebrun CM, Di Ciacca SR, Orlando K. Rowing injuries. *Sports Med.* 2005;35(6):537-555.

Silbert BI, Singer BJ, Silbert PL, Gibbons JT, Singer KP. Enduring efficacy of Botulinum toxin type A injection for refractory anterior knee pain. *Disabil Rehabil.* 2012;34(1):62-68.

Singer BJ, Silbert BI, Silbert PL, Singer KP. The Role of Botulinum Toxin Type A in the Clinical Management of Refractory Anterior Knee Pain. *Toxins (Basel).* 2015;7(9):3388-3404.

Singer BJ, Silbert PL, Dunne JW, Song S, Singer KP. An open label pilot investigation of the efficacy of Botulinum toxin type A [Dysport] injection in the rehabilitation of chronic anterior knee pain. *Disabil Rehabil.* 2006;28(11):707-713.

Singer BJ, Silbert PL, Song S, Dunne JW, Singer KP. Treatment of refractory anterior knee pain using botulinum toxin type A (Dysport) injection to the distal vastus lateralis muscle: a randomised placebo controlled crossover trial. *Br J Sports Med.* 2011;45(8):640-645.

Stephen JM, Urquhart DW, van Arkel RJ, et al. The Use of Sonographically Guided Botulinum Toxin Type A (Dysport) Injections Into the Tensor Fasciae Latae for the Treatment of Lateral Patellofemoral Overload Syndrome. *Am J Sports Med.* 2016;44(5):1195-1202.

Strauss EJ, Kim S, Calcei JG, Park D. Iliotibial band syndrome: evaluation and management. *J Am Acad Orthop Surg.* 2011;19(12):728-736.

Tater P, Pandey S. Botulinum toxin in movement disorders. *Neurol India.* 2018;66(Supplement):S79-s89.

Taunton JE, Ryan MB, Clement DB, McKenzie DC, Lloyd-Smith DR, Zumbo BD. A retrospective case-control analysis of 2002 running injuries. *Br J Sports Med.* 2002;36(2):95-101.

Tuite MJ. Imaging of triathlon injuries. *Radiol Clin North Am.* 2010;48(6):1125-1135.

Vastik M, Hok P, Hlustik P, Otruba P, Tudos Z, Kanovsky P. Botulinum toxin treatment of freezing of gait in Parkinson's disease patients as reflected in functional magnetic resonance imaging of leg movement. *Neuro Endocrinol Lett.* 2016;37(2):147-153.