Study Title: The Effect of Botulinum Toxin Injections on Ankle Dorsiflexion Following Internal Fixation of Tibial Plafond (Pilon) Fractures: A Pilot Study

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A. Specific Aims

Tibial plafond fractures account for 7-10% of all tibia fractures and are potentially devastating injuries that continue to provide treatment challenges for orthopaedic traumatologists. While most trauma centers have adopted a staged protocol with initial external fixation followed by delayed internal fixation after soft tissue recovery, patients continue to report relatively poor physical and psychosocial outcomes. A significant reduction in range of motion is commonly observed after operative fixation of tibial plafond fractures, specifically loss of dorsiflexion. If the decrease in dorsiflexion is severe enough, it is termed equinus contracture and can pose functional limitations and contribute to additional lower limb pathologies in those suffering from it. Botulinum toxin A has been shown to be effective in increasing dorsiflexion in children with equinus contracture from muscle spasticity from cerebral palsy. More recently, promising results have been seen in using Botulinum toxin A in the treatment of contractures following Achilles tendon repair and total knee arthroplasty. The purpose of this study is to evaluate the effect of Botulinum toxin A injections into the gastrocsoleus complex on ankle dorsiflexion following internal fixation of tibial plafond fractures.

Specific Aim 1: To determine if the use of Botulinum toxin A intramuscular injections of the gastrocsoleus complex in patients with operatively treated tibial plafond fractures will result in increased ankle dorsiflexion when compared to controls.

> Hypothesis 1: The group treated with Botulinum toxin A injections will have increased ankle dorsiflexion when compared to controls at 6 and 12 months.

Specific Aim 2: To determine if the use of Botulinum toxin A injections in patients with operatively treated tibial plafond fractures will lead to increased ankle functionality as measured by the FAAM, and quality of life as measured by the SF-36, when compared to controls.

> Hypothesis 2: The group treated with Botulinum toxin A injections will report more positive health-related quality of life when compared to controls at 6 and 12 months.

Specific Aim 3: To determine if the use of Botulinum toxin A injections in patients with operatively treated tibial plafond fractures will lead to a higher proportion of patients achieving at least 10 degrees of dorsiflexion when compared to controls.

> Hypothesis 3: The group treated with Botulinum toxin A injections will be more likely to achieve 10 degrees or more of ankle dorsiflexion at 6 and 12 months.

We plan to enroll 20 patients (N=10 treatment, N=10 controls) in a pilot study to test procedures and collect preliminary data. While this pilot study will likely not have sufficient power to definitively address the specific aims and hypotheses, the preliminary data collected will provide information to plan future work.

B. Background and Significance Defined as a fracture of the distal end of the tibia that involves a significant portion of the weight-bearing articular surface and overlying metaphysis, tibial pilon fractures are difficult orthopaedic injuries to treat. This fracture pattern is most commonly caused by motor vehicle collisions, falls, and sporting accidents.[1] These mechanisms produce high energy axial loads at the ankle joint causing significant articular comminution, bone loss, and soft tissue injury traditionally resulting in a high rate of unsatisfactory outcomes.[1,2]

B.1 Management of Pilon Fractures: Initially considered unsuitable for surgery, the treatment of tibial plafond fractures has evolved significantly over the last 50 years to a point where most centers are utilizing a staged fixation approach.[2-6] The staged method employs primary external fixation to restore length and alignment of the extremity while allowing the soft tissues to heal. Once the tissues permit, an open approach is used to provide sufficient visualization of the fracture for anatomic reduction of the articular surface and cancellous bone grafting if necessary. Rigid internal fixation with or without cancellous bone grafting is paramount in maintaining joint line congruity, preventing malunions, and allowing for early range-of-motion across the joint, thus providing better functional outcomes compared to other methods such as external fixation with or without limited internal fixation.[2,4-9]

B.2 Current Difficulties in Treating Pilon Fractures: Despite widespread usage of a staged protocol for this injury, good to excellent results are still difficult to attain. Recent studies consistently report "relatively poor physical and psychosocial outcomes" with persistent and severe sequelae.[6,9] Pollack and colleagues noted that at 3-year follow-up, patients presented with significantly poorer health related outcome scores than age and gender-matched norms.[6] Large proportions of patients with this type of injury present with significant stiffness, swelling, pain, and difficulties with retaining employment, showing that there is still work to be done to improve the outcomes of this devastating injury.[1,2,6,9-11]

B.3 Loss of Dorsiflexion: Limited range of motion is a common and potentially debilitating result of these often severe articular injuries. A minimum of 10 degrees of dorsiflexion is required for normal gait mechanics and loss of this dorsiflexion is termed equinus contracture.[12] Equinus contracture can result in functional limitations as well as be a contributing factor to seemingly unrelated lower limb pathologies including strains, plantar fasciitis, hallux valgus, stress fractures, adult-acquired flat foot, plantar fasciitis, Achilles tendonitis, Charcot arthropathy, diabetic foot ulceration, and metatarsalgia.[12,13,14] Gait analysis studies examining limited dorsiflexion in the ankle joint has shown that patients with less than 10 degrees of dorsiflexion begin to experience abnormal stresses at multiple other lower extremity joints.[13] In addition to contributing to these other pathologies, loss of dorsiflexion and pain are the only two independent variables shown to significantly limit functionality in patients recovering from ankle fractures.[15]

Recent studies following outcomes on tibial plafond fractures have repeatedly shown dorsiflexion to be impacted. Grose and colleagues found the average dorsiflexion in their cohort to be 9 degrees with only 25% achieving greater than 10 degrees of dorsiflexion.[16] Patients treated by Patterson and Cole achieved only 7 degrees of dorsiflexion after staged internal fixation.[5] Marsh et al. measured an average dorsiflexion of 10 degrees with 50% of patients failing to reach at least 10 degrees of dorsiflexion, even after excluding those who underwent amputation or arthrodesis.[11] Functional limitations such as difficulty climbing up stairs, walking up hills, and squatting to pick up objects are commonly reported problems following this injury, all of which reflect a loss of dorsiflexion.[6] Clearly, stiffness is a ubiquitous problem in this population and carries with it the sequela of impaired functionality while contributing to other lower extremity problems.

B.4 Treatment Options for Limited Range of Ankle Motion: Once acquired, equinus contractures can be very difficult to treat. Physiotherapy and stretching are the first line therapy to improve this condition, but often only play a limited role in the correction of this condition. Surgical options remain the mainstay treatment for contractures that are causing significant functional impairment. Achilles tendon lengthening is one surgical option that addresses equinus contracture by lengthening the Achilles tendon by utilizing a Z-lengthening technique. This procedure has a long recovery time and carries with it the risk of skin slough, Achilles tendon rupture, and discomfort with shoeware.[17] Because the Achilles tendon accounts only for 3-5% of the contracture,[14] there is also concern that lengthening the tendon reduces its moment-generating capacity due to the gastrocsoleus' new position on the sarcomere length-strength curve, resulting in weakness in plantarflexion.[18] Additionally, this procedure also carries with it the risk of over lengthening causing a profound loss of strength and resulting in a heel gait pattern.[19]

Other surgical options, such as the gastrocnemius recession, have been gaining popularity as an alternative to Achilles tendon lengthening in the treatment of equinus contractures, because it is able to address the contracture without resulting in loss of strength.[20] One such technique, termed the Strayer recession, is performed by separating the gastrocnemius from the soleus and transecting it just proximal to the gastrocnemius-soleus aponeurosis.[21] This allows the gastrocnemius muscle to retract proximally providing increased dorsiflexion.[21] This procedure produces excellent results by achieving an average increase in dorsiflexion of 14-18 degrees, but it is not without complications.[20,22] Sural neuropraxia is a common complication of this procedure, either due to excessive retraction on the nerve at the time of surgery or proximal and distal tethering of the nerve within the gastrocsoleus complex during the release.[23] Even though 42.5% of sural nerves run superficial to the facia effectively protecting them from laceration during the release, sural and saphenous nerve lacerations can and do occur.[23] Finally a significant number of patients report dissatisfaction with the scar left from the surgery which can pucker due to soft tissue adhesions, and exacerbated by retraction of the gastrocnemius muscle belly. Equinus contractures acquired after tibial plafond fractures are so problematic that some centers have advocated for performing a Strayer recession prophylactically at the time of fixation to prevent the development of such contractures.

B.5 Botulinum Neurotoxin: Botulinum toxin A (Botox) is an extremely potent neurotoxin produced by the bacterium *Clostridium botulinum* that results in transient flaccid muscle paralysis. To date, Botulinum toxin A and B are approved for use by the U.S. Food and Drug Administration for treatment of (1) chronic migraine headaches, (2) upper limb spasticity, (3) cervical dystonia, (4) strabismus and blepharospasm, (5) severe primary axillary hyperhidrosis, (6) and moderate to severe glabellar lines.[24] In the orthopaedic literature, multiple potential indications have been identified including shoulder dislocations, adhesive capsulities, talipes equinovarus, plantar fasciitis, torticollis, knee flexion contractures, lateral epicondylitis and cerebral palsy; all of which are currently considered "off-label."[25,26]

B.6 Botox Use for Treating Equinus Contractures: Among its many uses, Botox has been used in the treatment of a variety of range of motion limiting conditions. For many years, botulinum toxin has been used with great success in treating equinus deformity in children with cerebral palsy. Several double-blind prospective studies have reported an increase in ankle joint mobility during stance and swing phases with the use of Botox.[27,28]

Based on the success seen in the treatment of equinus contractures in children with cerebral palsy, botulinum toxin has been used in the treatment of equinus contractures following Achilles tendon repair. Reuter and others treated 8 patients with equinus contractures after Achilles tendon repair with intramuscular Botox injections and physiotherapy.[29] All patients experienced significant increases in dorsiflexion which remained present at their 2 year follow-up with no adverse events identified.[29]

B.7 Botox Use for the Prevention of Equinus Contractures: In addition to treating equinus contractures due to spasticity, Botox has been shown to prevent the occurrence of contractures in animal models. In 1994, Cosgrove and Graham used a spastic mouse model commonly used to mimic cerebral palsy, to show that intramuscular injections into the calf muscles prevented the formation of contractures. They found that mice who received placebo as opposed to intramuscular Botox had calf muscles which were 16% shorter than those who received Botox, supporting the theory of using Botox to prevent contracture formation.[30]

B.8 Botox Use for Treating Flexion Contracture Following Total Knee Arthroplasty: Recently, Botox has been used with great success in the treatment of flexion contractures following total knee arthroplasty. After an initial report on the successful treatment of flexion contracture following total knee arthroplasty in a patient with Parkinson's syndrome, Seyler and colleagues utilized botulinum toxin to treat 11 more patients with flexion contracture following total knee arthroplasty.[31,32] Their results were extremely promising by showing clinical improvement in all 9 patients who had primary total knee arthroplasties. The only two failures were in patients who acquired their contractures after *revision* total knee arthroplasties. The patients who experienced the improvement maintained their increased range of motion and desirable outcomes at the time of two year follow-up, leading the authors to conclude that Botox therapy may be appropriate therapy for the treatment of flexion contractures following primary total knee arthroplasty.[32] An additional investigation is currently under way using a larger cohort of patients and is currently showing promising preliminary results.[26]

B.9 Botox Reduces Pain and Spasm: Part of the theory on why Botox has been effective in alleviating these contractures is that the temporary muscle paralysis reduces pain and muscle spasms which can impede therapeutic stretching regimens. There is also increasing evidence that Botox has anti-nociceptive properties that may be due to inhibiting the release of pain mediators in addition to decreasing muscle spasms.[33] Muscle spasms are commonly experienced following fracture fixation and can be a source of significant discomfort, which can interfere with rehabilitation by causing pain and limiting range of motion. Neutralization of this phenomenon may result in better functional outcomes due to more effective rehabilitation and stretching techniques employed postoperatively.

Even after the initial spasms have subsided, Botox may aid in the prevention of contracture and help facilitate therapeutic stretching techniques by reducing the basal tone of the plantar flexors. Even at rest, muscles exert a baseline tone to maintain posture and joint position.[34] By weakening or paralyzing the gastrocsoleus complex, there would be an imbalance in muscular tone in the lower leg pulling the foot into a more dorsiflexed position even at rest. This will also reduce voluntary and involuntary guarding during stretching exercises, thus improving the effectiveness of rehabilitation regimens.

B.10 Summary: Based on Botox's ability to reduce pain and postoperative muscular spasms while at the same time eliminating resting basal tone of the primary plantar flexors about the ankle, it is felt that intramuscular injections will be beneficial in aiding therapeutic stretching exercises which is essential for maintaining ankle range of motion. These exercises will be started approximately 2 weeks after the time of definitive fixation which is well within the 8-10 weeks of maximal effect seen with intramuscular botulinum toxin injections.[29] Botulinum toxin injections have not only been shown to prevent the development in of contractures, but also used to treat contractures which have already formed.[27-32,35,36] The purpose of this study is to evaluate the effect of Botulinum toxin A injections into the gastrocsoleus complex on ankle dorsiflexion after staged internal fixation of tibial plafond fractures. If Botulinum toxin A proves effective, this approach could have a significant impact on the practice and outcomes of orthopaedic surgery and will allow for treatment and prevention of equinus contracture without the morbidity associated with an additional surgical procedure.

C. Preliminary Studies

While the investigators have not completed preliminary studies specifically addressing the effects of Botulinum toxin A on tibial plafond fractures, several members have had prior experience in prospective randomized studies in this patient population.

The principal investigator published a multicenter study entitled: "Indometacin as prophylaxis for heterotopic ossification after operative treatment of fractures of the acetabulum" which involved a similar prospective double-blind placebo-controlled study design.[37] The experience obtained from this study provides a valuable resource for successfully managing the proposed study.

The study implementation will be led by a PhD clinical researcher with experience coordinating randomized controlled trials funded by NIH, CDC, and the Robert Wood Johnson Foundation.[38-41] The principal investigator's orthopaedic clinical research team has successfully implemented and completed several randomized trials to date.

D. Research Design and Methods

We will use a prospective double-blind randomized placebo-controlled study design. Subjects will be enrolled as inpatients or during the initial office visit by orthopaedic clinical research staff. After routine evaluation reveals that a patient meets the inclusion and exclusion criteria (below), informed consent will be obtained. Demographic data will be recorded. Patients will be block randomized by opaque, sealed-envelope to either a treatment group or a placebo group (N=20; N=10 treatment, N=10 placebo).

D.1 Inclusion and Exclusion Criteria

Inclusion Criteria

- Patients 18 and older with a tibial plafond fracture to be treated by a staged protocol involving primary external fixation and definitive fixation within 3 weeks from the injury.
    - Non-definitive, interval procedures such as repeat irrigation and debridement and fibular fixation are allowed.

Exclusion Criteria

- Younger than 18 years of age.
- Significant traumatic brain injury or cognitive disability that would interfere with post-operative rehabilitation and study questionnaires.
- Nerve, vascular, or tendon injury of the lower leg: injury to the tibial or peroneal motor nerves, injury to the posterior tibial artery requiring repair, or laceration of tendons that are involved in plantar flexion or dorsiflexion of the ankle which require repair.
- History of prior lower extremity fracture to the tibia or ankle of the affected limb.
- Incarcerated patients.
- Patients unable or unwilling to return for follow-up examination.
- Pregnant or lactating patients.
- History of disease affecting the neuromuscular junction (ex: myasthenia gravis).
- Use of aminoglycoside antibiotics at the time of definitive fixation.
- Ipsilateral foot injury that will impair dorsiflexion exercises: Lisfranc injuries, fractures or dislocations of the talus, calcaneus, navicular, cuboid, cuneiforms, or metatarsals (phalanx fractures or dislocations will not be excluded).
- Patients receiving Botulinum Toxin A for other reasons.
- Patients with a known hypersensitivity to Botulinum toxin A.
- Gustilo Anderson type III B and C.
- Patients with a weight greater than 115 kg – to ensure proper injection locations.

- Patients taking non-depolarizing neuromuscular blocking agents (not including those used for general anesthesia).

D.2 Outcome Variables

Primary Outcome Variable (objective):

Ankle Dorsiflexion of Injured Extremity. The primary outcome variable will be ankle dorsiflexion of the injured extremity as measured by a goniomemeter and radiographs.

Ankle Dorsiflexion of Uninjured Extremity. In patients with a unilateral lower extremity injury, the ankle dorsiflexion of the uninjured extremity will be measured in the same fashion as the injured extremity.

Secondary Outcome Variables (self-report):

The Short-Form 36 (SF-36) will be used to measure health related quality of life. The SF-36 is a commonly used general health status measure and assessment of function, which allows individuals to describe their own health status. It allows for the comparison between individuals with the same condition as well as to the general population. Subscale scores measure various domains of health and quality of life, while the physical (PCS) and mental (MCS) component summary scores represent the main dimensions of health. The PCS and MCS scores range from 0 to 100 points and are standardized to population norms with higher scores indicating higher function. The mean score for the PCS and MCS in the general population is 50 points with 10 points representing one standard deviation from the mean.[52]

Pain. Overall Study limb as well as ankle specific pain intensity will be measured using the 0-10 *visual analogue scale* used in the Brief Pain Inventory. Pain intensity will be measured both at rest and during ambulation.[53] *The Brief Pain Inventory (BPI)* will be administered to patients at 6 and 12-month follow-up appointments. The BPI is a widely used, 15-item measure of pain intensity and interference with daily life.[53,54] The questionnaire assesses three key pain domains: pain intensity, pain interference, and efficacy of pain treatments or medications.

The Foot and Ankle Ability Measure (FAAM) is a well validated instrument that consists of 29 items measuring 2 broad categories: activities of daily living (84 points) and sports (32 points).[55] The scores are normalized to 100 for each category and are reported separately. The FAAM will be obtained at 6 and 12 months to assess the functional status of the affected ankle.

Independent Variables

Group Assignment: Participants assigned to the control group will receive normal saline injections following definitive fixation of their tibial plafond fracture (N=10). Patients assigned to the treatment group will receive Botulinum toxin A injections following definitive fixation of their tibial plafond fracture (N=10).

Covariates

Demographics

- Age
- Race/ethnicity
- Gender
- BMI

- Co-morbidities
- Fracture classification
- Time until definitive fixation
- Tobacco use
- Workers compensation status
- Level of education
- Marital status
- Personal income
- Health insurance
- Working status before injury

These data will be abstracted from the medical record by the research staff.

Additional Outcomes

- Time until full weight bearing
- Time until return to work
- Compliance with weight bearing status
- Compliance with prescribed treatment

These data will be patient reported

Complications

- Nonunion
- Malunion
- Infection: Deep
- Infection: Superficial
- Osteomyelitis
- Wound breakdown
- Skin slough: partial thickness
- Skin slough: full thickness
- Additional surgeries: Strayer recession, Achilles lengthening, hardware removal, amputation, or arthrodesis.
- Rehospitalizations

These data will be captured during clinical exam at each office visit

D.3 Methods

Orthopaedic surgery attendings and residents will identify potential study candidates during the initial consultation based on the presence of a tibial plafond fracture. If the patient meets the inclusion and exclusion criteria (noted above), a member of the treatment team will discuss the study with eligible patients. If the patient expresses interest in the study, the physician will notify the research staff. Orthopaedic Clinical Research staff will describe study procedures in detail and go through the informed consent process to enroll the patient in the study. Patients will be informed of the "off-label" usage of botulinum toxin injections as well as the potential side effects.

Once informed consent is obtained and the patient is enrolled in the study, the attending surgeon will classify the fracture based on the AO/OTA classification system (Figure 1). Study participants will then be block randomized and assigned by sequentially numbered sealed opaque envelopes to one of the two treatment groups based on computerized selection: those who receive intramuscular botulinum toxin injections at the time of definitive fixation, and those who receive placebo. Patients with bilateral pilon fractures and no other lower extremity injuries of the tibia, ankle, or foot that would further impair dorsiflexion stretching or other

rehabilitation exercises will have each extremity randomized and evaluated separately. Patients with a unilateral tibial plafond fracture and no injury of the contralateral tibia, ankle, or foot will be placed in a subgroup of patients who will have their unaffected extremity examined for comparison. Patients with an injury to the contralateral extremity that would exclude them from this subset will have only the extremity with the pilon fracture analyzed.

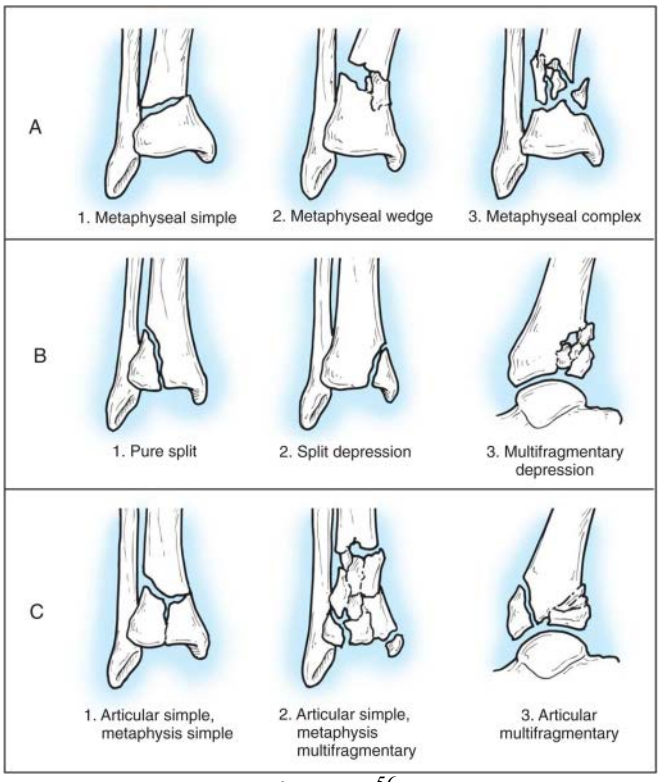

Figure 1.[56]

All patients will be treated by a fellowship trained orthopaedic surgeon who has completed advanced training in either trauma or foot and ankle surgery. Patients will all undergo a staged fixation approach which involves primary external fixation with irrigation and debridement if necessary, followed by open reduction and internal fixation when soft tissues allow. Additional procedures on the injured extremity that take place between external fixation and definitive fixation (ex: ORIF of the fibula or repeat irrigation and debridement) do not disqualify the patient from the study as long as definitive fixation takes place within 3 weeks (21 days) of the injury. All definitive operations will take place at either Carolinas Medical Center – Main, or Carolinas Medical Center – Mercy.

At the time of definitive fixation, the hospital's investigational pharmacy will provide a blinded solution of either Botulinum toxin A or 0.9% sodium chloride solution for injection intraoperatively following skin closure. Four syringes containing 0.5 ml 0.9% sodium chloride, with or without Botulinum toxin type A based on the patient's randomization, will be provided and refrigerated until they are ready to be administered. Both the physician and the patient will be blinded to the contents of the syringe. Once reconstituted, botulinum toxin type A will only last for 4 hours at room temperature so it will be necessary to not allow the solution to sit at room temperature for an extended period of time. All patients in the study group will receive onabotulinumtoxinA, Botox® (Allergan, Irvine, California) provided by the investigational pharmacy. The total dose of botulinum toxin will calculated based on the patient's weight in kilograms, such that a total dose of 200U of Botox will be used for a 70 kg individual (see Table 1 below). The dosage will scale linearly in

proportion to the patient's body weight, such that each kilogram change results in a 3U change in Botox (rounded to the nearest 30U interval change from 200U, with a maximum of 300U). This dosing regimen was chosen based on the effective dose for an average gastrocnemius from other studies.[26]

Table 1: Botox Dosing by Weight

45-55 kg:	140 U
55-65 kg:	170 U
65-75 kg:	200 U
75-85 kg:	230 U
85-95 kg:	260 U
95-105 kg:	290 U
105-115 kg:	300 U

At the completion of surgery, the gastrocsoleus complex will be injected in four locations (superior medial, superior lateral, inferior medial, and inferior lateral) prior to the application of short leg splint, per the recommendation of prior studies.[57] At each injection site, ¼ of the total dose of botulinum toxin A or normal saline will administered in approximately 0.5 ml injections. The use of EMG or other imaging modalities has been recommended to ensure accuracy of botulinum toxin injection at the target muscle motor end plates, however it is not necessary when injecting the gastrocsoleus complex, even in small children due to its large size and superficial location.[58] The injection sites are illustrated in the figure 2 below:

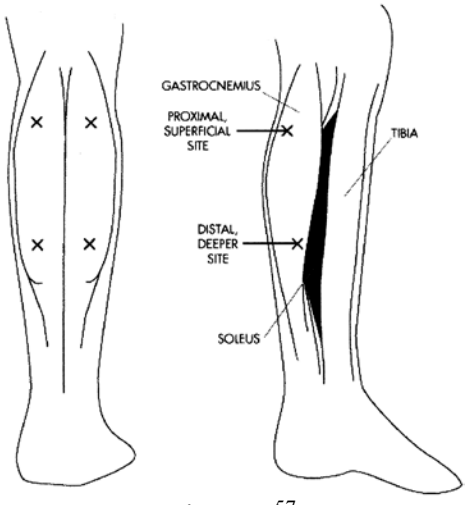

Figure 2[57]

Following definitive fixation and study injections, patients will be placed in a well-padded splint in at least neutral dorsiflexion for two weeks to allow for wound healing. Following wound healing, patients will transition to a removable orthosis and begin range of motion exercises and stretching techniques. All patients will undergo a structured exercise regimen. Each patient will receive a pamphlet at an 8th grade reading level containing a standardized exercise protocol which clearly states the exercises to be utilized, the frequency, and duration. As long as there are no adverse events, patients will proceed to touch down weight bearing at roughly 6 weeks postoperatively and continue their exercise program. Patients will then advance to partial weight bearing at approximately eight weeks and full weight bearing as tolerated at 10 to 12 weeks, as long as no adverse events occur precluding this progression.

Study participants will return to regularly scheduled follow-up appointments to monitor their progress. At each follow-up appointment (2 weeks, 6 weeks, 12 weeks, 6 months, and 1 year), patients will be monitored for signs and symptoms of Botox toxicity. All patients will be seen in follow-up at one of two clinic locations. At each site, research staff familiar with the study will be present along with a device for measuring dorsiflexion in a standardized fashion.

Clinical assessment will be accomplished by physical exam and questionnaires for subjective complaints described above with a member of the Orthopaedic Clinical Research staff. Patients will be asked to complete SF-36, BPI, and FAAM questionnaires at their 6 month and 12 month follow-up visits. Time to full weight bearing, time to return to work, compliance with weight bearing status, and compliance with rehabilitation protocol will all be noted at 6 and 12 months.

At the end of the 6 and 12-month follow-up appointments, ankle dorsiflexion will be assessed using a device to measure dorsiflexion and radiographcs in a standardized manner.

Routine radiographs taken as part of standard of care will be used to assess the quality of fracture alignment, range of motion and to follow for boney union or malunion. Radiographic data will be reviewed by a group of three independent observers blinded to the patient and the treatment group. Malunion will be assessed by drawing a line along the subchondral bone of the tibial plafond and a line drawn through the center of the tibial shaft. Deviation of >5 degrees from 90 in either the AP or lateral plane will be considered varus, valgus, or sagittal plane malunion. Clinical union will be defined as the patient's ability to bear full weight on the injured extremity with evidence of boney bridging in at least 2 of 4 cortices. The determination of nonunion will be determined by the attending surgeon's assessment based on radiographic and clinical findings consistent with nonunion, such as hardware failure, failure of boney bridging, and persistent pain at the fracture site beyond what would be expected in a healed fracture.

Study volunteers will be provided with a $70 patient incentive for their time in completing the health assessment questionnaires and dorsiflexion measurements at 6 months. An additional $100 will be provided to those who return at 1 year for examination and health assessment questionnaires.

The results of the patients receiving Botox will be compared to those who received placebo. Average dorsiflexion will be determined and compared between the two groups as well as the percentage of patients who achieve 10 degrees or more of dorsiflexion. If applicable, the average dorsiflexion in the injured extremity will also be compared to the uninjured extremity to determine the average difference in dorsiflexion between the two groups. For statistical analysis, differences with a p value of <0.05 will be considered statistically significant.

D.4 Data Management

All data will be entered into REDCap, a web-based data entry and management system that provides logic checks on input and checks for invalid entries. Data will be entered continuously as they are collected and stored in univariate form. We will also run standard checks for outliers, duplicates and other types of errors which may occur within a complex data file. All data files will be password protected and hard copies of blinded patient records will be maintained in locked cabinets in the research office.

Data Analysis: In order to determine that the randomization process produced comparable groups, we will use t-tests and cross-tabulations to compare patients in the treatment group to patients in the placebo group on the following variables: age, race, gender, BMI comorbidities, fracture classification, time until definitive fixation, tobacco use, workers compensation status, level of education, marital status, personal income, health insurance, working status before surgery, compliance with weight-bearing restrictions, compliance with prescribed treatment, time until full weight bearing and return to work.

Analyses will follow the intent-to-treat paradigm, under which all patients will be analyzed according to the treatment group to which they were randomized. Intention to treat analyses of outcomes will be conducted in two stages. First, we will conduct a bivariate analysis to examine relationships between assigned treatment

group, primary and secondary outcomes, and potential covariates and confounders (demographics, injury characteristics, co-morbidities). We will then use the results to build a multivariate model to predict primary and secondary outcomes based on treatment type.

D.5 Pilot Data

Currently, no previous work has been done on this project and therefore no pilot data is available. If funding for the entire study is unable to be secured, partial funding will be used for the procurement of pilot data. A pilot study will consist of 20 patients, 10 randomized to each group, and will be executed in the same manner as the full trial. A pilot study will show that the investigators and research staff are capable of implementing this prospective, double-blind, placebo controlled trial which will serve to strengthen further external grant proposals. At the conclusion of the pilot study, blinding will be broken and the data will be analyzed. Those data will be used to support or modify the power analysis for the full study and will eventually be incorporated into to the full study cohort. If clearly inferior results are observed in the intervention group, those data will be published and the full trial will not be conducted.

D.6 Estimated Timeline

Due to the large number of trauma patients treated at our institution, a retrospective review of the number of cases indicates an incidence of 108 tibial plafond fractures treated per year. With an expected enrollment rate of 60% and a goal sample size of 20 patients, we expect enrollment to take 4 months, making this study quite feasible.

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Train research staff on study procedures												
Train surgeons on dorsiflexion measuring device												
Patient Enrollment												
Patient Follow-up at 6 and 12 months												
Data Analysis												
Manuscript development, submission, and preparation of final report												

D.7 Potential Problems

In a busy trauma center, the enrollment of patients in prospective randomized study can be difficult. We will train the attendings, fellows, residents, and our research staff to identify potential candidates for the study. Information about the study including the inclusion/exclusion criteria will be readily available online or on study information cards provided to the staff and residents. Additionally, all surgical staff will receive an in-service training session so that they are aware of the study protocol to be followed in the operating room. There will be approximately 14 days between the time of injury and definitive fixation giving ample time for patient identification and obtaining informed consent.

D.8 Future Directions

At the conclusion of this pilot study, the data collected will be unblinded and analyzed. Those data will be used to aid in a power analysis to determine the sample size needed for a full trial. This protocol will then be amended to include the appropriate number of patients needed to be enrolled in order to have the appropriate

power. If no changes are made to the protocol, the data from this pilot will be combined with the data of the full study cohort.

E. Human Subjects

E.1 IRB Statement

As this study involves the inclusion of live human subjects and their personal information, we will strictly follow the guidelines and procedures outlined by our institutions IRB. Ensuring patient safety and maintaining patient confidentiality are of paramount importance and taken extremely seriously by the investigators of this study.

E.2 Study Population

All subjects involved in this study will be ages 18 and older who have sustained a fracture of the tibial plafond. All patients will have their injury treated in a staged protocol, meaning primary external fixation followed by definitive fixation within 3 weeks of the injury.

Inclusion Criteria

- Patients 18 and older with a tibial plafond fracture to be treated by a staged protocol involving primary external fixation and definitive fixation within 3 weeks from the injury.
    - Non-definitive, interval procedures such as repeat irrigation and debridement and fibular fixation will be allowed

Exclusion Criteria

- Younger than 18 years of age.
- Significant traumatic brain injury or cognitive disability that would interfere with post-operative rehabilitation and study questionnaires.
- Nerve, vascular, or tendon injury of the lower leg: injury to the tibial or peroneal motor nerves, injury to the posterior tibial artery requiring repair, or laceration of tendons that are involved in plantar flexion or dorsiflexion of the ankle which require repair.
- History of prior lower extremity fracture to the tibia or ankle of the affected limb.
- Incarcerated patients.
- Patients unable or unwilling to return for follow-up examination.
- Pregnant or lactating patients.
- History of disease affecting the neuromuscular junction (ex: myasthenia gravis).
- Use of aminoglycoside antibiotics at the time of definitive fixation.
- Ipsilateral foot injury that will impair dorsiflexion exercises: Lisfranc injuries, fractures or dislocations of the talus, calcaneus, navicular, cuboid, cuneiforms, or metatarsals (phalanx fractures or dislocations will not be excluded).
- Patients receiving Botulinum Toxin A for other reasons.
- Patients with a known hypersensitivity to Botulinum toxin A.
- Gustilo Anderson type III B and C.
- Patients with a weight greater than 115 kg – to ensure proper injection locations.
- Patients taking non-depolarizing neuromuscular blocking agents (not including those used for general anesthesia).

E.3 Inclusion of Women and Minorities in Study

The study population will be representative of the typical trauma population seen at Carolinas Medical Center – Main. Carolinas Hospital System is the largest provider in the region with a large catchment area encompassing western North Carolina and South Carolina. As the region's busiest trauma center, patients of all ages, genders, ethnicities, and backgrounds present to CMC, which is representative of the diverse population enjoyed by this region of the country. Women and minority groups will all be included in the study. Based on previous clinical series of patients at our institutions, we expect that 70% of our patients will be men and 25% minority patients.

E.4 Description of the Screening Procedures and Recruitment Process

Potential patients will be recruited during the index hospitalization or as a referral from an outside physician. Patients that may be eligible for the study will be evaluated by the attending physician to determine whether the inclusion and exclusion criteria are met. An attending surgeon will approach patient about volunteering for the research study, and if patient expresses interest, the formal education and consent process will be initiated by research staff. The research assistant or coordinator will then discuss the research and enrollment process and consent patients expressing willingness to participate.

E.5 Description of the Informed Consent Process

Once a patient has expressed interest in the study, a member of the treatment team will provide each patient with sufficient time and information to make a well-informed decision on whether or not to enroll in the study based on the risks and benefits imposed. There are strong ethical and practical reasons for striving for quality in the consent process and is taken seriously by all those involved in this study. Decisions made hastily or without accurate and adequate information are not in the patient's or the investigators' interest. Materials to inform prospective participants and to obtain consent will be developed in conjunction with the Steering Committee and consultants as required to ensure that they are accessible, informative and culturally sensitive.

Persons who meet the initial eligibility criteria for the study will be told of the trial, its purpose, and the general expectations of those enrolled. Those interested in further screening and willing to participate will be given a copy of the consent. Formal consent, as represented by the act of signing and dating an IRB approved consent statement for the trial, will occur after the final evaluation for eligibility and a review of what is involved in the trial. Persons will be reminded of the expectations placed on them if they enroll. They will be advised not to enroll if they are uncertain that they would be willing to accept treatment as assigned by a random process. Ambivalent subjects should not be enrolled. Persons will be given an opportunity to query study personnel on issues needing clarification. Patients who no longer wish to be involved in the study will be withdrawn immediately at their request and continue to receive the standard of care.

E.6 Risk/Benefits Assessment

E.6.a Foreseeable Risks: There are minimal risks inherent in this study. Both study arms will receive the current standard of care in the treatment of their tibial plafond fractures. The treatment group, however, will receive intramuscular injections of botulinum toxin A; an indication which is considered "off-label" as it is not an FDA approved indication of the product. Botox has been used safely and effectively for many years for similar "off-label" indications in the orthopaedic literature. Great care was taken to ensure that Botox is used safely and correctly in this study. All effects of Botox are completely reversible if given enough time, and it is felt that botulinum toxin injections will pose minimal risk to patients when used correctly.

5.6.a.1 Botulinum Toxin Safety

Botulinum Toxin A has been approved by the FDA for more than 20 years and has a long-established safety profile. When used correctly, the side effects of Botulinum Toxin type A injections are uncommon and usually mild and transient.[59] Local side effects are the most common and are usually mild pain at the injection site and adjacent muscle weakness due to diffusion of the toxin across fascial barriers.[25] Systemic side effects are very rare and include mild generalized weakness, urinary incontinence, constipation, and dysphagia; all of which are typically seen in susceptible individuals.[25] Botox is contraindicated in patients with a history of neuromuscular disorder such as myasthenia gravis, and in patients receiving aminoglycoside antibiotics or non-depolarizing neuromuscular blocking agents, as these can all potentiate the effects of the toxin. It is also relatively contraindicated in patients with a history of pseudobulbar palsy and frequent chest infections for concern over aspiration pneumonia, an exceedingly rare, but serious side effect. These adverse events are not expected to cause problems based on our study design and patient population.

Of the local side effects, pain at the injection site is unlikely to be noticed by the patient as injections will be administered under general anesthesia and the patient's co-committent injury will likely dwarf any residual pain from the injection. The diffusion of Botox into adjacent muscle groups is not only inconsequential, but in-fact desired based on our study design. Although all injections will be made in the muscle belly of the gastrocnemius, diffusion into the deeper soleus muscle would provide additional weakness of the gastrocsoleus complex and potentially result in better outcomes without causing additional functional impairment

In order to minimize the occurrence of systemic side effects, the amount of Botox utilized in this study will be well below the maximum safe dose for Botox, 12U/kg, even if bilateral pilon fractures are both randomized to the treatment group.[57] In addition, patients with a history of a neuromuscular disorder, who are receiving aminoglycoside antibiotics or non-depolarizing neuromuscular blocking agents, or women who are or may become pregnant will be excluded from this trial. Patients reporting dysphagia or aspiration are typically those undergoing injections for cervical dystonia, and may be considered a local side effect rather than a systemic one. Based on the remote injection site utilized for this study, dysphagia and aspiration are unlikely to be experienced. The average total dose of 200U of Botulinum Toxin A will be injected into the gastrocnemius of the effected extremity and was chosen based on the effective dose for the average gastrocnemius from other studies.[26]

E.6.a.2 Duration of Botox

An intramuscular injection of Botox results in flaccid paralysis that gradually improves over an average of 2 to 4 months.[25,60,61] Although the effects are temporary, paralyzing the primary plantar flexors in the lower leg could prove problematic and result in gait disturbances contributing to subsequent falls. For this reason, pilon fractures have been chosen for this study because it is an injury which not only commonly results in ankle stiffness, but it also requires a non-weight bearing status for approximately 3 months, allowing the botulinum toxin to run its course without interfering with return to normal function. The effects of Botox are entirely reversible over time, and long term effects are unlikely to be experienced.

E.6.b Foreseeable Benefits: The specific aims of this study are to provide improved outcomes of operatively treated tibial plafond fractures by using Botox to improve ankle dorsiflexion. Patients randomized to the Botox arm of the study have the potential to experience increased ankle dorsiflexion, which will result in improved gait and lower limb functionality, as well as reduce the risk of developing other lower extremity pathologies.

E.7 Patient Safety Monitoring

A data safety monitor will be appointed for this study. This person will otherwise be uninvolved in the planning or execution of this trial but will have the ability to unblind the collected data to analyze and determine if subjects experiencing an unacceptably high level of adverse events. The adverse effects of Botox are typically mild, transient, and well tolerated by most patients. Additionally, most side effects of Botox are commonly seen at baseline in the trauma population being studied (ex: generalized weakness, constipation, difficulty with urination, etc). For this reason, only adverse events outside of what would reasonably be expected for a typical post-operative trauma patient will be considered. These adverse events will be assessed by the treating physicians at every follow-up appointment (2 weeks, 6 weeks, 3 months, and 6 months), who will notify the data safety monitor within 24 hours. If deemed necessary, the data safety monitor will unblind the collected data and determine if the study group is experiencing adverse events at a significantly higher rate or with greater severity than the control group. If the risk to patients is deemed unacceptably high by the data safety monitor, the study will be terminated and the results will be published.

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