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Efficacy of a single botulinum toxin A injection for distal tarsal tunnel syndrome: A protocol for a randomized, double-blinded trial

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ABSTRACT

Introduction: Distal tarsal tunnel syndrome (DTTS) is characterised by compression of the tibial nerve as it passes underneath the abductor hallucis muscle belly. There is no current consensus on treatment for DTTS. This study was conducted to compare and evaluate the effect of ultrasound-guided botulinum toxin A (BTX-A) versus ultrasound-guided corticosteroid injection (CSI) for the treatment of DTTS.
Methods: This study was a single-centre, randomized, and double-blinded trial. The study protocol was submitted to the local ethics committee board and subsequently registered in a research registry. 88 patients with DTTS were randomly divided into 2 groups according to the treatment received. The patients were evaluated over 12 weeks. Evaluation was via the Foot Health Status Questionnaire (FHSQ). The primary outcome measures were pain and the secondary outcomes were function and the use of oral analgesics. All of the assessments were performed at baseline and at 3, 6, and 12 weeks after treatment.
Results: This is a randomized controlled trial evaluating the efficacy of BTX-A versus CSI in the treatment of DTTS. This study has limited inclusion and exclusion criteria and a well-controlled intervention.
Conclusions: The results of this trial will provide more evidence on which method can better treat DTTS.
Trial registration: We have registered this trial with the Australian New Zealand Clinical Trials Registry and the temporary trial number is 380,105.

1. Introduction

Distal tarsal tunnel syndrome (DTTS) was first described in the 1960s by Kech et al. [1] and Lam et al. [2] and is characterised by compression of the tibial nerve as it travels underneath the abductor hallucis muscle into the plantar aspect of the foot. This compression occurs through fibrosis and/or thickening of the osteo-fibrous structures, or spasticity of the abductor hallucis muscle [3]. DTTS causes deep plantar foot pain, especially after extended periods of weight-bearing [4]. The true incidence of DTTS is unknown, with 50% of cases appearing to be idiopathic [5].

Although its pathogenesis is unclear, risk factors may include pathological foot biomechanics, intrinsic muscle weakness, extended periods of standing, higher body mass index (BMI), and foot deformities such as pes planus [6,7]. Unlike plantar fasciitis where individuals experience first-step pain, DTTS symptoms are exhibited after extended periods of standing or walking [8]. The diagnosis is usually made on the basis of patient history and clinical findings. Physical examination may identify pain upon palpation of the abductor hallucis muscle just distal to the heel.

There is currently no consensus regarding treatment. Treatments may include physical therapy, corticosteroid injections, non-steroidal anti-inflammatory drugs (NSAIDs), orthotics and surgical decompression [4]. Recently, advances in the treatment of musculoskeletal disorders with botulinum toxin A (BTX-A) have been documented [9]. The aim of this trial will be to investigate whether BTX-A can reduce DTTS symptoms by reducing the compression caused by the abductor hallucis muscle belly on the underlying nerve. To our knowledge, no study to date has investigated this.

BTX-A has been used for the treatment of musculoskeletal pathology, including plantar fasciitis [9]. The mechanism of action involves the blocking of acetylcholine at the neuromuscular junctions, resulting

Abbreviations: CSIcorticosteroid injectionBTX-Abotulinum toxin A injectionVASvisual analog scaleDTTSdistal tarsal tunnel syndromeFHSQfoot health status questionnaire

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in muscular paralysis, and the proteolysis of SNARE proteins that are involved in the release of various neurotransmitters [9].

Corticosteroid injections (CSI) are commonly used in the treatment of various heel pain syndromes. However, there have been reports of complications with CSI. Rupture of the plantar fascia has been reported to occur in 2.4–5.7% of patients and, despite the pain relief associated with a rupture, resultant instability of the lateral column with calcaneocuboid joint pain has been observed [10,11].

The aim of this study is to compare the effectiveness of injections of botulinum toxin A and corticosteroid at reducing pain associated with DTTS over a 12-week period.

2. Method

2.1. Design

This is a double-blind randomized controlled trial comparing botulinum toxin A (experimental) with corticosteroid (control) injections for the treatment of DTTS with a 12-week follow-up period. The flowchart of this trial is shown in Fig. 1.

2.2. Participants and setting

This trial will be conducted at two private radiology practices and will recruit local community-dwelling participants via referral from victorian podiatrists, podiatric surgeons, and medical practitioners. Participants will be required to have a least a 6-month history of pain within the distal tarsal tunnel prior to enrolment. Participants must report a minimum pain magnitude of 20 mm on a 100 mm visual analog pain scale (VAS).

Clinically, participants must exhibit sensitivity and an appreciable stiffness of the abductor hallucis muscle upon palpation. A friend or family member will be required to attend for their second visit (during which the injection is given) to provide transportation from the clinic.

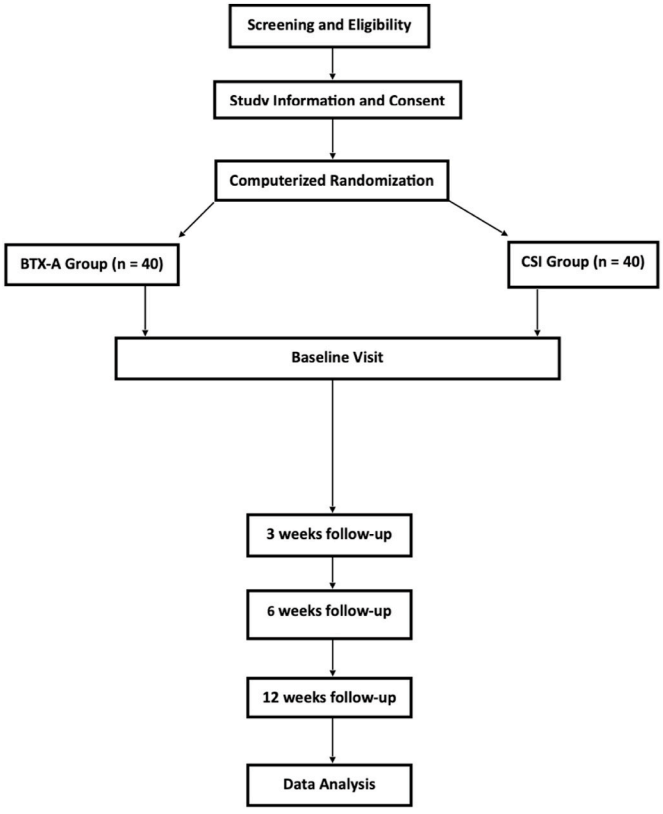

Fig. 1. Flow diagram of the study.

Applicants will be excluded if they have received or experienced any of the following: Hypersensitivity to local anaesthetics, hypersensitivity to corticosteroids, hypersensitivity to botulinum toxin, a current skin or soft tissue infection in the proximity of the injection site, current pregnancy, systemic inflammatory disease, or previous local surgery. Applicants will also be excluded if they are unable to walk household distances without the use of an aid, or if they have commenced any treatment regiment for distal tarsal tunnel syndrome within the 4 weeks prior to their enrolment.

Screening of applications according to the above criteria will occur by a preliminary telephone interview, followed by a clinical examination at the initial visit. After a detailed explanation of the study protocol, eligible applicants will be invited to participate. Prior to enrolment, all applicants will be assessed for competence to give consent by use of the Evaluation to Sign Consent (ESC) tool [12]. A range of descriptive characteristics will be collected at the initial visit after enrolment. Participants will then be scheduled for a second appointment (approximately one week later) where baseline measurements will be taken and the trial intervention performed.

2.3. Randomisation, allocation concealment and blinding

Treatment allocation will be performed according to a computer-generated randomized number sequence. Allocation was concealed in a password protected computer file accessible by an investigator not involved in measuring outcomes (SRE). All investigators were blinded to the treatment allocation throughout the study.

OB prepared the syringes prior to injection, thereby ensuring the investigator giving injections (BJT) and measuring outcomes and analysing data (SRE) were blinded throughout the trial duration. Both treatment solutions (i.e. botulinum toxin and betamethasone sodium acetate) will be masked with opaque syringes. This protocol will also ensure that trial participants are blinded to their treatment allocation.

2.4. Interventions

Participants will be randomly allocation to one of two treatment arms: (i) ultrasound-guided injection of the distal tarsal tunnel with BTX-A (experimental group), or (ii) ultrasound-guided injection of the distal tarsal tunnel with CSI (control group). Participants will be positioned in the lateral position on the treatment table depending on the side being injected (i.e. left lateral position for left DTTS). The BTX-A injection will be administered into the abductor hallucis muscle belly at the widest point in cross-section under ultrasound with a 25 gauge (38 mm) needle and a 1 mL Luer-lock syringe containing 50 units of botulinum toxin and 2 mL of 2% lignocaine hydrochloride. The control injection will be administered into the abductor hallucis muscle belly at the widest point in cross-section under ultrasound with a 25 gauge (38 mm) needle and a 1 mL Luer-lock syringe containing 1 mL (5.7 mg) betamethasone sodium acetate and 2 mL of 2% lignocaine hydrochloride. For both injections, the needle will be inserted through the distal tarsal tunnel perpendicular to the long axis of the ultrasound transducer, and will be advanced under continuous guidance into the abductor hallucis muscle belly. An aseptic injection technique will be used to minimise infection risk, including the use of sterile gloves and sterile transmission gel. Participants with bilateral distal tarsal tunnel syndrome will have both feet treated (with their allocated intervention) during a single appointment. Following treatment, participants will be advised to avoid high impact activities for at least 2 weeks post-injection.

2.5. Instrumentation

The primary outcome will be pain at 3, 6 and 12 weeks. Pain will be measured by the foot pain domain of the Foot Health Status Question-

naire (FHSQ), which has been shown to have a high degree of internal consistency and test-retest reliability (intra-class correlation coefficient = 0.86) [13]. Participants treated for bilateral distal tarsal tunnel syndrome will be asked to describe symptoms without specific reference to an individual foot (i.e bilateral pain will be evaluated as one independent sample).

Secondary outcomes will be function and use of oral analgesic medication. Function will be measured by the foot function domain of the FHSQ, which has been shown to have a high degree of internal consistency and test-retest reliability (intra-class correlation coefficient = 0.92) [13]. Participants treated for bilateral distal tarsal tunnel syndrome will be asked to describe foot function without specific reference to an individual foot (i.e. bilateral function will be evaluated as one independent sample). Use of oral analgesic medication (including paracetamol, aspirin, opioids, and non-steroidal anti-inflammatory drugs) will be recorded at each visit.

2.6. Adverse events

Complications and adverse events associated with the intervention (e.g. infection, nerve injury or skin depigmentation) will be recorded in participant files and reported in the final manuscript.

2.7. Sample size calculation

A prospective sample size calculation indicates a sample of 44 participants per group (i.e. 88 in total) would provide 80% power to detect a minimal important difference (MID) of 12 points [14] on the pain domain of the FHSQ (SD = 20, alpha = 0.05, 5% loss to follow-up).

2.8. Recruitment

Recruitment of participants commenced on September 1, 2020 and is expected to continue until September 2021.

2.9. Statistical analysis

Statistical analyses will be undertaken using SPSS software (version 14.0 or later, SPSS Corporation, Chicago, Il, USA). Continuous data will be explored for normality using standard tests to satisfy the assumptions of parametric statistics. All analyses will be conducted on an intention-to-treat basis and missing follow-up data will be replaced with baseline observations carried forward (BOCF) (i.e. baseline data will be carried forward in circumstances where follow-up observations are missing). In comparison to a last observation carried forward (LOCF) approach, BOCF has been shown to provide a more conservative estimate when analysing the treatment effect of pain-relief medication [15]. Continuous outcomes with a normal distribution will be analysed using a linear regression technique with baseline measurements adjusted for by the analysis of covariance model (ANCOVA) [16]. If data is found to be not normally distributed, transformation will be attempted. However, if data is still not normally distributed after transformation, non-parametric tests will be used. Other data (nominal or ordinal) will be analysed using appropriate non-parametric statistical tests. Statistical significance for hypothesis tests will be set at the conventional level of 0.05.

2.10. Ethics consideration

The La Trobe University Human Ethics Committee will be approached to approve this trial. Ethical standard will adhere to the National Health and Medical research Council (NHMRC) National Statement [17] and the World Medical Association's Declaration of Helsinki [18]. Publications associated with the trial will be formatted according to the CONSORT Statement [19].

3. Conclusion

Plantar foot pain with a diagnosis of distal tarsal tunnel syndrome is a common disorder presenting to podiatry clinics. Despite this, there appears to be no randomized controlled trials on clinical treatment options. This trial aims to provide evidence as to the efficacy of a single injection of botulinum toxin at reducing pain associated with this condition. The outcomes of this trial may influence practice guidelines and clinical care in this area.

This trial will be limited by the lack of a gold standard treatment that may be used within the control group. This trial is also limited in its ability to teat different combinations of treatment options as there are many varied treatment options available.

There is a significant lack of available research evidence supporting the theorised pathomechanics and the efficacy of available treatment options in the treatment of conditions such as distal tarsal tunnel syndrome. This creates a degree of uncertainty for clinicians and researches attesting to pursue an evidence-based treatment approach. This trial may help clinical to better understand this condition and the efficacy of treatment options available.

Authors' contributions

OB conceived the study idea. SRE designed the trial protocol. SRE drafted the protocol manuscript. OB and SRE are the chief investigators. OB and BJT commented on the draft manuscript. All authors assisted in designing the trial protocol and commented on the draft manuscript. All authors read and approved the final manuscript prior to submission.

Consent or assent

All participants will provide written informed consent prior to enrolment.

Declaration of competing interest

The authors declare that they have no competing interests.

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