Botulinum A toxin versus external fixator in the management of diabetic foot ulcer

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Received 3 April 2016
Accepted 20 April 2016

The Egyptian Orthopaedic Journal
2016, 51:47–53

Objective
The purpose of this study was to describe the use of dermal fillers in the treatment of large, soft-tissue defects in diabetic foot with and without the use of external fixation of the foot.
Patients and methods
Thirteen patients with chronic nonhealing diabetic foot ulcer for several weeks to months were included in the study. There were 11 male and two female patients. Seven patients (three female and four male) were randomly assigned to the Botox injection group, and six patients (four female and two male) were randomly assigned to the external fixator group. The mean ± SD age of patients was 55 ± 10 years.
Results
At 12 weeks, the proportion of healing was significantly higher in the Botox with an external frame group than in the Botox alone group (89.5 vs. 61.4%, $P = 0.026$). At final follow-up, 12 (92.3%) patients were ambulatory with a regular or custom shoe and had a good result based on our defined criteria. There were no complications from the injections.
Conclusion
The use of Botox together with an external fixator is an attractive choice to off-load diabetic foot ulcer.

Keywords:
botulinum A, diabetic foot ulcer, external fixator

Egypt Orthop J 51:47–53

1012-5574

Introduction

Wound healing remains a dilemma in many clinical situations, especially in compromised patients such as diabetic patients with ulcerations or complicated infections. In clinical situations involving acute/chronic infections, the accompanying small vessel thrombosis often progresses to the point where simple debridement is not sufficient [1]. Delays in ambulation during prolonged conservative treatment may result in deconditioning, which may be difficult to overcome. In patients with chronic peripheral edema and an insensate foot, distal skin grafting may result in troublesome verrucous hyperplasia and graft breakdown. Other closure methods such as adjacent toe fillet flaps and local rotation flaps are viable options, but carry second-site morbidity and may impart a problematic local healing burden. In addition, certain patients simply may refuse these procedures. In this subset of patients with difficult defects, rapid closure would be ideal, saving time and resources and allowing patients to ambulate sooner [2]. Extensive wounds following trauma or osteomyelitis in the diabetic foot and ankle frequently demand creative techniques for sound reconstruction. Diabetic patients can experience multiple complications to the lower extremity as a result of chronic ulcerations, contiguous osteomyelitis, and Charcot neuroarthropathy, establishing a unique reconstructive challenge [3].

Techniques to achieve a rapid defect closure have included serial tightening of transosseous metatarsal wires with local care and subsequent split-thickness skin grafting 3; more recently, external fixation devices have been used. Although the concepts of soft-tissue closure can be traced back to the teachings of Ilizarov, more recent applications of external fixation for closure of foot defects have been published [4,5]. In the case of diabetic studies, patients who underwent surgery to lengthen the Achilles tendon had reduced risk for ulcer recurrence. Lengthening the Achilles tendon or heel cord (TAL) weakened the calf muscle and diminished the pressure on the ball of the foot where ulcers occur [6,7]. TAL causes a temporary reduction in forefoot pressure primarily by reducing plantar flexion power during gait. The initial decrease in forefoot pressure, followed by progressive reloading of forefoot

tissues as plantar flexion muscles regain strength after TAL, may help reduce the risk for ulcer recurrence in patients with diabetes [8].

Botulinum A toxin is now widely used for the treatment of a variety of conditions characterized by muscle hyperactivity, and is increasingly being seen as a valuable treatment option in the management of spasticity. Since the first publication on using botulinum toxin in 1993 [9], it has become increasingly common to use the botulinum toxin A in the injection of the muscles responsible for the dynamic deformation of club foot; most teams now typically inject muscle groups other than the triceps surae frequently with multisite injections [10]. Botulinum A toxin, injected into a muscle, causes temporary paralysis of the muscle, lasting about 3–6 months [11]. The site of action is at the nerve terminals. Botulinum A toxin blocks the release of acetylcholine by the synaptic vesicles. Recovery occurs by terminal sprouting of the nerves [12]. Reports on the use of botulinum A toxin in the lower extremity muscles of patients with cerebral palsy have supported the concept that improvement in muscle balance can be produced with injections into dominant spastic muscles [13]. The intramuscular botulinum toxin A injection in cerebral palsy children with ankle plantar flexor spasticity can objectively reduce the spasticity and yield improvements in the sagittal plane kinematics at the ankle and in the Gross Motor Function Measures, which declined at 8 weeks without any serious side effects [14]. With this concept in mind we can postulate that botulinum A toxin injection could perform the same action of TAL.

The purpose of this study was to describe the use of dermal fillers in the treatment of large, soft-tissue defects in diabetic foot with and without the use of external fixation of the foot.

Patients and methods

The study was designed according to the recommendations of the IHS, and was approved by ethical committee of school of medicine Tanta University. A written informed consent was obtained from all participants prior to study commencement. Patients were randomly assigned to participate in one of the two treatment groups: Botox (Allergan; Botox 100IU 1 vial Allergan 1Vial Active ingredients: CLOSTRIDIUM BOTULINUM From Dawaya, Egypt) injection followed by immobilization in total contact cast or application of an external fixator frame.

Study design and data sources

All patients enrolled for the study had chronic nonhealing diabetic foot ulcer for several weeks to months. These patients were evaluated on a weekly basis. Among the patients enrolled for the study ($n=13$), there were 11 male and two female patients.

Patients were considered for inclusion in this controlled clinical trial if they had a history of diabetes mellitus (DM), loss of protective sensation (unable to sense a 5.07 Semmes–Weinstein monofilament on at least one location on the plantar surface of the foot) [15], maximal passive dorsiflexion range of motion (DF-ROM) of 5° or less, and a recurrent or nonhealing forefoot ulcer (Wagner scale grade II) [16]. A limitation of 5° of DF-ROM was chosen because most authors believe that at least 10° of DF-ROM is required for normal ambulation [17]. A recurrent or nonhealing ulcer was defined as at least the second occurrence of a plantar ulcer or previous failure to heal a plantar ulcer with the use of total contact casting (TCC).

Patients were excluded for consideration if they would not benefit from a Botox injection procedure (i.e. were nonambulatory), had a history of cerebrovascular accident or other neurological problem complicating their rehabilitation, had a history of hind foot Charcot fractures, or had an ankle–arm index less than 0.45 (to rule out severe vascular problems). We did not exclude mid-foot or forefoot Charcot deformities or partial foot amputations.

Patients were divided into two groups after the application of dermal fillers to large, soft-tissue defects in the diabetic foot: one with and the other without the use of an external fixation of the foot. Volunteers of group I were subjected to wound-care assessment and evaluation of balance, muscle strength, sensory skills, and heel bone density. They received Botox injections in the calf muscle during one study visit. Group II was also subjected to the same together with adding external fixation of the foot.

Thirteen patients met the study inclusion criteria and agreed to participate.

Seven patients (three female and four male) were randomly assigned to the Botox injection group, and six patients (four female and two male) were randomly assigned to the external fixator group. The mean ± SD age of the patients was 55 ± 10 years, and female sex was predominant (seven female and six male). Type 2 DM was predominant (nine patients with type 2

DM and four patients with type 1 DM), with a mean ± SD duration of 19 ± 12 years. All patients had severe peripheral neuropathy and lacked protective sensation as evidenced by a history of a plantar ulcer and the inability to sense the 5.07 Semmes–Weinstein monofilament on at least one location on the plantar surface of the foot [15].

Group I received gastrocnemius–soleus muscle injections on the involved side with 300-U of Botox ($n = 5$, weight = 129 ± 22 kg). Botox dose was converted to U/kg. The majority patients received between 1.9 and 2.4 U/kg ($n = 11$) and one patient received 3.2 U/kg.

The medical records of these patients were reviewed for the following factors: sex, height, weight, BMI, social history, associated comorbidities, index injury or deformity, initial surgical procedures, the length of time that the frame remained in place, and postoperative complications. The final position of the foot to the leg and final ambulatory status were established as the endpoints of this study. Treatment groups were not significantly different with regard to age, ethnicity, BMI, duration of DM, HBA1c, sex composition, or the proportion of patients with type 1 and type 2 DM (Table 1).

The patients' final ambulatory status was characterized as either walking without assistance, or mobilizing with the use of a brace, crutches, cane, wheelchair, or other supportive device. The ultimate outcome was established at the time of latest clinical follow-up.

Major complications such as deep venous thrombosis, pulmonary embolism, myocardial infarction, deep-space infection, osteomyelitis, neurovascular injury, malunion, nonunion, tibial stress fractures, compartment syndrome, reflex sympathetic dystrophy, amputation, or death were recorded. Minor complications, including pin-tract infection, pin-site irritation, stiffness, pain, impalement of musculotendinous structures, and broken hardware, were excerpted from the medical record as determined by the operating surgeon.

Table 1 Demographic characteristics and clinical outcome measures for Botox injection and external fixator groups

	Botox	External fixator	*P*
Sex (F/M)	3/4	4/2	0.68
Age (years)	54.2 ± 9.0	54.3 ± 9.9	0.98
BMI (kg/m^2)	34.1 ± 5.9	31.8 ± 6.8	0.34
Type of DM (type 1/type 2)	3/4	1/5	0.42
Duration of DM (years)	20.4 ± 10.6	17.9 ± 13.9	0.58
HbA1c (%)	8.7 ± 1.7	8.9 ± 2.0	0.80
Healing rate [*n* (%)]	7/7 (100)	5/6 (83.3)	NA
Healing time (days)	43 ± 18 (61.4%)	50 ± 36 (89.5%)	NA
Ulcer recurrence rate [*n* (%)]	1/7 (14.2%)	0/6 (0%)	NA

Values are given as mean ± SD. Ulcer recurrence rates at 8 month follow-up. DM, diabetes mellitus; F, female; M, male; NA, not applicable for purposes of study.

Injection technique

Botulinum toxin A (Botox; Allergan) was injected through 21 G needles that were Teflon coated except for the tip; these were also used as EMG electrodes. Botulinum toxin A, diluted with saline to a concentration of 10 U/0–1 ml, was injected at two sites close to the motor point. The point was identified using standard neurophysiological techniques. The toxin was injected only when either a continuous or stretch-induced EMG activity was recorded; otherwise, another injection site in the vicinity was checked. In all patients, the soleus, tibialis posterior, and medial and lateral head of the gastrocnemius muscles of the affected side were treated with a total dose of 400 U of Botox (100 U = 1 ml of fluid each). After the Botox injection, partial weight bearing was allowed, and after the first week the patient progressed to full weight bearing but was asked to limit his or her activities as much as possible.

Surgical technique

As with treatment of any diabetic foot or ankle wound, the medical status of the patient should be optimized preoperatively. Comorbidities of diabetes, particularly peripheral vascular disease and peripheral neuropathy, should be addressed because these have a significant effect on wound healing. Vascular assessment of the lower extremities should include the ankle-brachial index, the toe-brachial index, Doppler waveforms, and pulse volume recordings to determine whether a vascular surgical consultation is warranted to improve perfusion. Formal surgical debridement of infected wounds should be performed along with appropriate antibiotic therapy assigned on the basis of intraoperative cultures.

Once the recipient's wound has undergone proper extensive irrigation and debridement to remove all necrotic and nonviable tissue, the foot is then placed inside of a foot plate from the Ilizarov external fixation system with the plantar aspect of the foot parallel to the long axis of the foot plate when viewed from a lateral view. A distal tibial ring may be used during the procedure to increase the frame stability, especially during the tensioning technique and on weight sharing. The hind foot and/or distal tibia are then stabilized with several crossed olive wires placed

through standard pedal safe corridors about the calcaneus and talus. Next, one olive wire is placed from medial to lateral at the level of the metatarsal bases and another is placed from lateral to medial again at the level of the metatarsal bases. Simultaneous tensioning of 60–90 kg of these wires allows for precise and gradual closure of the soft-tissue defect and foot deformity.

The patient is seen weekly for dressing changes and wire site care, which consists simply of cleansing the foot, ankle, and lower limb and external fixation device with sterile saline, followed by application of povidone–iodine solution-soaked gauze wrapped around each pin-site and generous application of gauze pads 'fluffed' and placed about the space created between the foot, ankle, and lower leg and the external fixation device. A simple ACE wrap (*ACE*^{TM} Brand Elastic Bandag) is then placed about the proximal lower leg to limit edema in this area and circumferentially around the external fixation device to limit the patient's direct view of the device and improve 'tolerance' during the fairly short recovery process while still permitting weight sharing through a modified postoperative shoe application. The external fixation device is usually removed once wound has healed at the 4–6 week time frame and appropriate postoperative shoe and brace therapy is initiated on an indefinite basis.

Concomitant medications prescribed were insulin and other oral hypoglycemics, such as second-generation sulphonylurea, glycephase, metformin, and glipizide, and appropriate systemic/topical antibiotics. The systemic antibiotics prescribed were third-generation antibiotics such as cephalosporin, oxazolidinones, clindamycin, fluoroquinolones, meropenem, metronidazole, and amino glycosides, whereas topical application antibiotics prescribed were mupirocin, betadine, and fucidin.

Patients in the external fixator group were allowed to fully bear weight immediately after initial application of the frame. The ankle was positioned as close to neutral as possible until the plantar ulcer was healed. Patients were then instructed to wear their extradepth shoes with custom-molded inserts. There was no difference in days immobilized between the two groups.

Primary outcome measures were related to ulcer healing. Ulcers were considered healed when they showed complete epithelialization with no drainage. Ulcers were evaluated in each group every 7–14 days by the physician as the casts were changed for the first group and during outpatient clinic visit every week for the second group. Ulcer healing (yes or no) and the time to healing (days) were recorded for each patient. Patients were considered to have ulcer recurrence if the ulcer reopened (a break in the epithelial tissue and drainage) in any location in the forefoot.

Results

Descriptive characteristics for the subgroups are listed in Table 1. No significant differences were observed in any of the characteristics evaluated, including age, sex, duration of diabetes, size or location of wounds, or duration of plantar wounds. With the numbers available, we could not detect a difference in wound healing based on sex ($P=0.15$) or degree of glucose control ($P=0.78$). However, healed wounds were smaller at baseline compared with unhealed wounds (1.1 ± 1.0 vs. $1.9 \pm 1.3\,cm^2$, $P=0.02$).

The proportion of healing in patients treated with Botox alone and in those with Botox with an external frame was 89.5 and 65.0, respectively. At 12 weeks, the proportion of healing was significantly higher in the Botox with external frame group than in the Botox alone group (89.5 vs. 61.4%, $P=0.026$). There was also a significant difference in cumulative wound survival at 12 weeks between patients treated with Botox together with an external frame and those treated with Botox alone ($P=0.033$). Among patients with healing within the 12-week period, the mean time to healing was significantly shorter in patients treated with Botox together with an external frame than in those treated with Botox alone (33.5 ± 5.9 vs. 61.0 ± 6.5 days, $P=0.005$). No falls or device-related ulcerations were reported during the course of study.

Activity of the patients was also measured. Patients treated with Botox together with an external frame were significantly less active (600.1 ± 320.0 daily steps) than those treated with Botox alone (1461.8 ± 1452.3 daily steps, $P=0.04$).

There were 11 men and two women. The average age of the patients at surgery was 54.3 years (range: 26–66 years). Most patients were obese with an average BMI of 31.8 kg/m^2 (range: 19.4–50.8 kg/m^2), and an average weight of 210 lb (range: 110–375 lb). Four patients had type 1 and nine had type 2 DM, with an average HgA1C of 8.7 and 8.9, respectively. Three patients were active smokers at the time of surgery.

Circular wire frames were generally fashioned with two rings above and two rings below the ankle when

possible and secured with a combination of half-pins and tensioned olive or smooth wires. Time to frame removal averaged 96.1 days (range: 48–299 days).

Postoperative follow-up averaged 9.6 months (range: 6.1–13.1 months), including clinical assessment visits and radiographic evaluation. Two (15.4%) patients developed one major complication in our series, resulting in a major complication rate of 7.7% in 13 cases.

One of the patients underwent a below-knee amputation. Osteomyelitis and/or deep-space infection occurred in one (7.7%) case and was subsequently treated with serial debridement and parenteral antibiotics. None of our cases required a free flap or skin graft for coverage. There was one (7.7%) below-knee amputations that occurred secondary to intractable infection.

There were no incidences of neurovascular insult, pulmonary embolism, deep venous thrombosis, myocardial infarction, or compartment syndrome. The major complication rate was relatively higher for smokers and patients with an increased BMI.

At final follow-up, 12 (92.3%) patients were ambulatory with a regular or custom shoe and had a good result based on our defined criteria. There were no complications from the injections.

Discussion

The goal of any treatment for the diabetic foot is to create a plantigrade, stable, and shoeable/braceable foot and/or ankle that will be free of significant risk for further breakdown, ulceration, and/or infection [18].

It is reported that 15% of individuals with diabetes will develop at least one foot ulcer during the lifetime [19]. Sensory loss and mechanical stress are the primary risk factors of foot ulcers [20–22] and repetitive walking stress is considered the most common mechanism of injury [21]. Plantar ulcerations develop over areas of highest pressure [20,23], and the off-loading of stress is considered essential for wound healing [24].

A variety of methods have been recommended to off-load foot ulcerations [25–27]. Numerous studies have shown the effectiveness of the total contact cast in reducing foot pressure and in promoting wound healing [28,29]. The total contact cast is considered the gold standard or the most effective method in healing foot ulcers [30].

Many factors can contribute to plantar ulcers in diabetic patients, but the two major factors are believed to be angiopathy and neuropathy. Neuropathy is currently recognized as the primary factor leading to plantar ulceration [31,32]. Levin [31] describes the sequence of ulceration secondary to neuropathy involving sensory, motor, and autonomic nerve fibers. Sensory loss can allow painless trauma, and motor neuropathy can lead to muscle atrophy and foot deformity, which causes increased pressure on parts of the insensitive foot [32]. Autonomic neuropathy leads to decreased perspiration, which causes dry, cracking skin. Brand has long emphasized the role of decreased sensation and concurrent increased, repetitive mechanical pressures as principal causative factors of ulceration [32]. Several studies have reported successful healing of diabetic plantar ulcers in the presence of vascular disease through the use of total contact casting [33,34], a method that reduces the mechanical pressure at the site of ulceration. Limited dorsiflexion could result in increased pressure on the forefoot, particularly during the late stance phase of gait [35]. Because the Subtalar joint (STJ) has been described as important in the absorption of transverse rotation and impact of the lower extremity during gait, limitations in this joint could place increased stress on the plantar skin surface [35].

The results supported our primary hypothesis that both Botox injection and external fixator helps ulcer healing and to reduce ulcer recurrence rate compared with total contact cast alone. The time period of greatest risk for ulcer recurrence in the total contact cast treatment method was the initial 3 weeks after treatment. We believe that a primary reason for the lower rate of early recurrence was that peak pressure on the forefoot was substantially reduced after the injection or the application of the external fixator similar to what happened with TAL. The lower forefoot pressure may allow the ulcer to heal more thoroughly. Further studies are required to prove these findings.

The role of external fixation in the surgical treatment of the acutely unstable or chronically malaligned and/or ulcerated diabetic foot remains a matter for conjecture because of the paucity of peer-reviewed, scientifically sound, and meaningful studies available [36–38].

Everyone has heard of Botox being used to reduce the appearance of fine lines and wrinkles, but now the

muscle-immobilizing treatment is moving to the opposite end of the body and providing remarkable benefits that are getting patients back on their feet.

In many cases the most effective way of treating diabetic foot ulcers is to apply casting on the foot. This removes the pressure off the foot and helps the ulcers to heal. However, foot ulcers often return once the casting is removed and the patient starts walking with shoes on again. Healing the ulcers is tough, but keeping them healed is tougher.

The skin on the foot is not strong enough to handle the pressure during walking, and the same pressure points are at risk for ulcerating again. Thus, Botox helps in relaxing the tension on the foot, giving it a more stable position. Botox weakens the muscles and blocks nerve signals that cause the muscles to contract. Because when one has a foot injury or ulcer, he or she tends to avoid walking on the painful area, and instead walks on the ball of the foot. This would aid in wound healing and would have adequate off-loading so that there is no added pressure on the wound site. Injection of the Botox into specific locations in the calf and the feet to loosen the muscles in the area provides the pressure point relief. When one receives Botox injections, the Botox causes the muscles to respond and push one forward as one walks, which prevents any pressure or pain from developing under one's foot. The muscles recover from Botox in 2–3 months, giving the wound the time to fully heal [39].

Once the Botox begins showing its effect, either bracing or casting of the foot can be carried out to provide stability and flexibility within that foot; thus, the patient has the chance to walk normally again.

The results of this study suggest that Botox together with an external fixator frame heals a higher proportion of wounds in a shorter amount of time compared with Botox alone. In addition, it seems that patients are less active when treated with Botox together with an external fixator. This reduction in activity and ability to aggressively off-load the plantar aspect of the foot may partially explain the success of the Botox with an external fixator. Generally, peak plantar pressures are highest in the forefoot, whereas they tend to be of a lower magnitude in the rear foot and medial arch. However, the most important attribute of Botox together with an external fixator may be its ability to 'force compliance'. The patient has little choice other than to adhere to the regimen prescribed by the clinician, because the device is not easily removable. Furthermore, on the basis the results of the present study, it seems that Botox together with an external fixator may significantly curtail activity, thereby reducing the number of cycles of repetitive stress on an already open wound. In addition, external fixator allows patients, family members, or healthcare providers to assess the foot or wound on a daily basis. Therefore, advanced wound healing modalities that require daily applications would be suitable for use with patients using a nonremovable device such as the external fixator. Finally, external fixator generally is indicated for wounds with soft-tissue infections or osteomyelitis.

The above-described advantages make Botox together with an external fixation an attractive choice to off-load the diabetic foot ulcer. However, there are a number of potential negative detractors that may dissuade some clinicians from using this modality. Most clinics do not have a physician or external fixator technician with training or experience to safely apply an external fixator. Besides, improper external fixator application can cause skin breakdown and, in some cases, even frank ulceration, which can be a most unappealing characteristic. In addition, many patients experience problems with activities of daily living, such as bathing and sleeping. Moreover, certain designs of external fixators may exacerbate postural instability. Any one of the above reasons may compel the clinician to elect to use devices other than the external fixator for off-loading the wound for a given patient. In addition, one may argue that upfront costs for the treatment of wounds with an external fixator are higher. However, one may argue that a significantly faster healing time would negate the added cost in supplies.

Conclusion

The use of Botox with external fixator is an attractive choice to off-load the diabetic foot ulcer. However, similar to the use of external fixation for foot and/or ankle deformity correction, it is a complicated process with multiple patient and physician opportunities for. In conclusion, this study suggests that there are significant differences in wound healing based on the off-loading device selected. There is no single off-loading device that is appropriate for every patient. It is for this reason that we hope that work will continue in this area to assess various treatments to provide the clinician with the evidence necessary to make informed treatment decisions. It is in this manner that we believe we may realize more consistent wound healing and, commensurately, a meaningful and

widespread reduction in the rate of amputations of the lower extremity.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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