Botulinum toxin and hyperhidrosis of the amputation stump in war amputees

Toxine botulique et hyperhidrose du moignon d'amputation chez les amputés de guerre

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Abstract

Introduction: Stump hyperhidrosis is a common condition after lower limb amputation. It affects the prosthesis use, and the quality of life of patients. Several case reports tried to prove benefit of using Botulinum toxin in its treatment.
Aim: This study was to conduct a larger workforce clinical trial and to demonstrate benefits of botulinum toxin injection in the treatment of stump hyperhidrosis.
Methods: A prospective study was conducted. War amputees who complained of annoying excessive sweating of the stump were included. They received intradermal injection of botulinum toxin A in the residual limb area in contact with prosthetic socket. Abundance of sweating and degree of functional discomfort associated with it were assessed before, after 3 weeks, 6 and 12 months.
Results: Seventeen male patients, followed for post-traumatic limb amputation were included in the study. Discomfort and bothersome in relation to Hyperhidrosis did decrease after treatment (p<0,001). Reported satisfaction after 3 weeks was 73,33%. Improvement of prothesis loosening up after 3 weeks was 72,5% [±15,6]. Mean injection-induced pain on the visual analogue scale was 5.17/10 (±1.58). The mean interval after the onset of improvement was 5.13 days [min:3, max:8]. The mean time of improvement was 10.4 months after the injection [min:6, max:12]. No major adverse events were reported following treatment.
Conclusions: Intradermal injections of botulinum toxin in the symptomatic treatment of stump hyperhidrosis are effective and have few adverse effects. It improves the quality of life of our patients thanks to a better tolerance of the prosthesis.

Key word: War amputees, Hyperhidrosis, stump amputation

Résumé

Introduction: L'hyperhidrose du moignon est une affection courante après l'amputation d'un membre inférieur. Elle affecte l'utilisation des prothèses et la qualité de vie des patients. Plusieurs études de cas ont tenté de prouver l'avantage de l'utilisation de la toxine botulique dans son traitement.
Objectif: Cette étude visait à mener un essai clinique plus large et à démontrer les avantages de l'injection de toxine botulique dans le traitement de l'hyperhidrose du moignon chez les amputés de guerre.
Méthodes: Une étude prospective a été menée, incluant les amputés de guerre qui se plaignaient d'une transpiration excessive et gênante du moignon. Ils ont reçu une injection intradermique de toxine botulique A dans différentes zones du moignon en contact avec l'emboîture prothétique. L'abondance de transpiration et le degré d'inconfort fonctionnel qui y est associé ont été évalués avant, après 3 semaines, 6 et 12 mois.
Résultats: Dix-sept patients de sexe masculin, suivis pour amputation post-traumatique d'un membre, ont été inclus dans l'étude. L'inconfort et la gêne liés à l'hyperhidrose ont diminué après le traitement (p<0,001). La satisfaction rapportée après 3 semaines était de 73,33%. L'amélioration du déchaussement de la prothèse à 3 semaines était de 72,5% [±15,6]. La douleur moyenne induite par l'injection sur l'échelle visuelle analogique était de 5,17/10 (± 1,58). L'intervalle moyen après le début de l'amélioration était de 5,13 jours [min : 3, max : 8]. Le délai moyen d'amélioration était de 10,4 mois après l'injection [min : 6, max : 12]. Aucun événement indésirable majeur n'a été signalé après le traitement.
Conclusions: Les injections intradermiques de toxine botulique dans le traitement symptomatique de l'hyperhidrose du moignon sont efficaces. Elles améliorent la qualité de vie de nos patients grâce à une meilleure tolérance de la prothèse.

Mots clés: Amputés de guerre, moignon d'amputation, hyperhidrose

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Introduction

The skin represents the contact interface between the prosthesis (socket) and the amputation stump in amputee patients. A lesion or an anomaly in the skin therefore affects the prosthesis' use, and the quality of life of these patients (1). One of the most frequently reported complaints is hyperhidrosis (excessive sweating) of the amputation stump. It concerns up to 72% of patients (2). This complaint has multifactorial origin: sympathetic nervous system dysregulation (post-traumatic or post-operative), reduction in the cooling surface of the amputated limb, trapping of sweating inside the socket which does not evaporate normally, thermoplastic or carbon socket which leads to excessive local heat… Added to these factors is climate. Indeed, the Tunisian weather is notably hot in the summer. Temperatures varies between 25 and 35° Celsius for this season.

Patients' quality of life is closely linked to comfortable use of the prosthesis. Several therapeutic options have been explored, but they were either not very effective or even presenting annoying side effects leading to their rejection by patients. As a matter of fact, topical antiperspirants, such as aluminum chloride, must be reapplied frequently and can cause skin irritation. Oral pharmacological treatment, with anticholinergic drugs, has significant side effects, such as dry mouth, tachycardia, and cognitive disorders (concentration and memory). And finally, surgical procedures including sympathectomy and sweat gland removal are reserved for extreme cases of hyperhidrosis and are often accompanied by scars or infection. (3–5)

Using botulinum toxin for the treatment of hyperhidrosis dates to the 90s, after a decrease in sweating was observed in patients with botulism. Then over the years, its use in the treatment of hyperhidrosis has become more democratic thanks to the aesthetic medicine (armpits, sweaty palms, etc.). Botulinum toxin would act by blocking the release of acetylcholine in the postganglionic sympathetic fibers of the sweat glands (6). But beyond its aesthetic use, several attempts have been made to prove its benefit in the treatment of excessive sweating of the amputation stump. But most of these studies were case report (7–9), not allowing this therapeutic practice to be generalized.

The aim of this study was to conduct a clinical trial with a large workforce and to demonstrate benefits of botulinum toxin injection in the treatment of stump hyperhidrosis, especially in a specific Tunisian hot climate.

Methods

This is a prospective, and descriptive study, which was carried out at the Department of Physical Medicine and Rehabilitation (PMR), between June 2020 and September 2022. Were included all the war amputee patients followed in the PMR department, who complained spontaneously or during the guided questioning of annoying excessive sweating of the amputation stump. War amputees were chosen because the institution provides them with full financial care support, and in particular botulinum toxin, which remains relatively expensive in Tunisia. Our study did not include patients with contraindications to botulinum toxin use such as: pathology of the neuromuscular junction (myasthenia, Lambert-Eaton syndrome), pregnancy and breastfeeding, known hypersensitivity, and injection site's infection. Patients who had not completed the entire therapeutic protocol were excluded.

Patients received an injection of botulinum toxin from the amputation stump to the upper edge of the socket or liner. The botulinum toxin used was type A, marketed under the name Botox® (Botox, Allergan, Inc., Irvine, CA). In fact, it is the only specialty which has obtained marketing authorization from the FDA and the French National Agency for Medicines and Health Products for the use of botulinum toxin in axillary hyperhidrosis, and it's available in Tunisia. No product to our knowledge has obtained Marketing Authorization in hyperhidrosis of the amputation stump or other localization. Botulinum toxin (100U) was diluted with 4 mL of 0.9% sterile physiologic saline. The choice of the administered dose was made according to the recommendations of the FDA which in axillary hyperhidrosis indicate the total dose in adults at 100 units and based on studies subsequently published (7–9). The dose that should not be exceeded for all indications (spasticity, detrusor overactivity, etc.) is 300 units in adults according to the product instructions itself. It was injected intradermally in 40 points (0.1 ml per injection point), using a 4 mm long needle. A preliminary grid pattern of the skin (5 rows x 8 columns) was made to have an equal distribution of the treatment (Figure 1). It was covering the surface area of the patient's residual limb that normally is in contact with his prosthetic socket, in a circumferential manner.

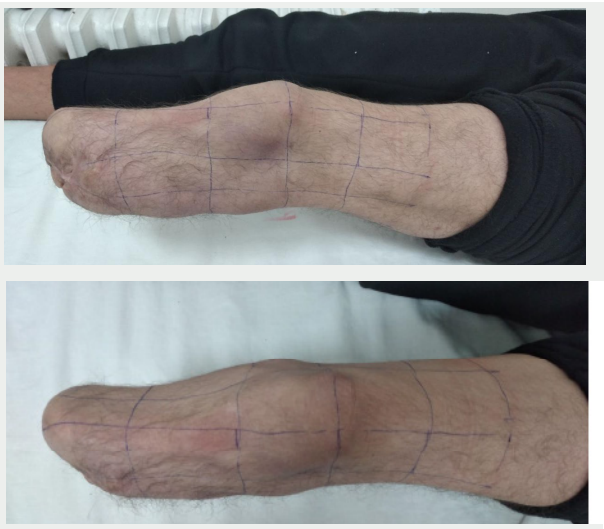

Figure 1. Grid (5 lines x 8 columns) for injection of botulinum toxin into the amputation stump

When the patient presented dermic lesions due to hyperhidrosis or cutaneous abrasion related to the prosthesis (Figure 2), these lesions were first treated. Then the patient was called back to receive the injection of botulinum toxin when the skin healing was complete.

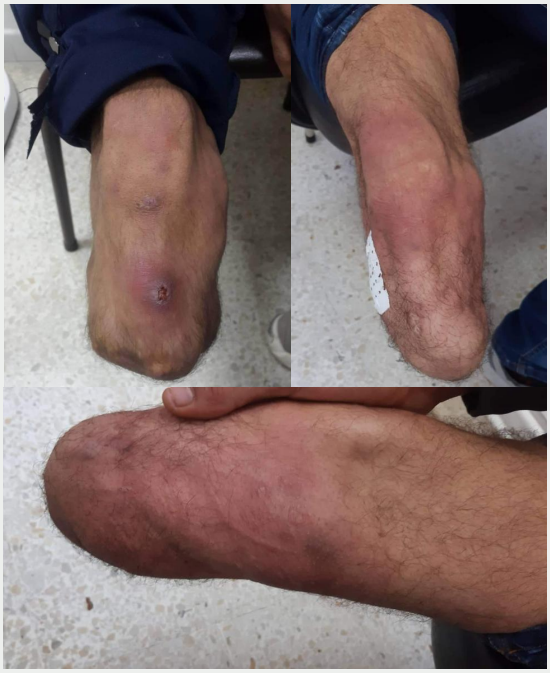

Figure 2. Cutaneous lesions of the residual limb related to hyperhidrosis (folliculitis and dermatitis)

Complaints attributed to hyperhidrosis were evaluated before and after injection of botulinum toxin. The discomfort caused by hyperhidrosis was also assessed by the Likert scale (1: none, 2: moderately, 3: severely) and the visual analogue scale (VAS). The evaluation was made again 3 weeks after the injection. The degree of discomfort and the impact due to hyperhidrosis were reassessed. Patient satisfaction with treatment was noted. Patients also reported the interval after onset of improvement. Then the patients were contacted by telephone at 6 months and 12 months post injection to determine the time of effectiveness of the injections over time.

No anesthesia was used prior to the injection, and patients were also asked to report pain due to the procedure.

Statistical analysis

Summary statistics for patients were calculated as means and ± standard deviations for the continuous variables and frequencies (percentages). Statistical analysis of the data was carried out using a two-way ANOVA for repeated measures followed by uncorrected paired Student's t-test in comparing data at each time point.

Ethical considerations and disclosure of interest

We declare to have no conflict of interest with the study. Full written informed consent was obtained from all participants. The approval of the hospital's ethics committee has been obtained.

Results

Fifty male patients were followed at the PMR department for post-traumatic limb amputation (following an anti-personnel mine explosion). The median age is 27.5 ± [25; 32.75] years with extremes ranging from 22 to 49 years. Among the 50 subjects enrolled, 17 reported spontaneously or during the interview a bothering hyperhidrosis of the amputation stump. They were therefore included in the study, in the absence of non-inclusion criteria. Among the twenty-three acts of botulinum toxin injection, six were reinjections spaced 12 months apart.

Table 1 shows sociodemographic characteristics of patients.

Table 1. Baseline demographics and clinical patients' characteristics

Baseline demographics and clinical patients' characteristics: 17 patients		
Age (years)	Median	29
	Mean	30,83
	Standard Deviation	5,82
Mean years since amputation		3,96
Practicing physical activity (%)	Yes	28
	No	72
Return to work (%)	Yes	22
	No	78

65% of the patients already had a special gel liner (Alpha SmartTemp®, WilloWood, USA), designed specifically to reduce excessive sweating inside the socket. The complaints related to hyperhidrosis reported by patients were maceration (56.5% of patients), loosening of the prosthesis (78.3% of patients) and folliculitis (30.4% of patients).

Botulinum toxin injection improves significantly stump hyperhidrosis. The results are summarized in Table 2.

Table 2. Clinical outcome variables determined at baseline and 3 weeks post-treatment.

	At baseline (Mean ± Standard deviation)	**3 weeks after treatment (Mean ± Standard deviation)**	**p**
Levels of Discomfort in relation to Hyperhidrosis (Likert 0-3)	3,00 ±0	1,17 ±0,48	<0,001
VAS bothersome in relation to hyperhidrosis	7,83 ±0,56	3,00 ±1,28	<0,001
Satisfaction (%) reported by patients after 3 weeks		73,33 [±8,6]	
Improvement (%) of hyperhidrosis reported by patients after 3 weeks		71,25 [±14,73]	
Improvement (%) of loosening up reported by patients after 3 weeks		72,5 [±15,6]	
Interval (in days) after the onset of improvement		5,08 [±1,34]	
Persistence of improvement (in months) reported by patients		10,50 [±1,84]	

We did not find any statistically significant difference in terms of improvement in sweating according to the number of injections (1st or 2nd injection).

Pain induced by the injection was rated by the patients on average on the visual analogue scale at 5.17/10 (±1.58). The mean interval after the onset of improvement is estimated at 5.13 days [min: 3, max: 8]. The mean time of improvement is estimated by patients at 10.4 months

after the injection [min: 6, max: 12].
No major adverse events were reported following botulinum toxin injection.

Discussion

This present study indicated that administration of botulinum toxin type A is highly effective in symptomatic treatment of stump hyperhidrosis.

Published studies

In the past decade, several researchers have sought to determine if the use of botulinum toxin is effective in amputation stump hyperhidrosis. It was mostly published as case report, listing 1 to 9 patients (7–11). Nevertheless, there is a randomized controlled trial published in 2015, which compared the effect of the toxin in 9 amputees versus placebo in 4 other patients (12).
The etiologies of amputations with hyperhidrosis which benefited from botulinum toxin are multiple. In addition to the traumatic origin, as is the case for our work, the vascular etiologies (10), metabolic (diabetes) (13) or even post infectious (osteomyelitis) (7) were also cited.
The complaints related to hyperhidrosis treated by toxin injection are the same as those found in our work. Dermatological lesions are the most frequently cited (9,14). The mismatches of the prostheses particularly during hot weather periods, intense professional activity or in sports activities are also found (15). these mismatches can even cause falls when walking (8). There are specific scales, such as The Hyperhidrosis Disease Severity Scale, which assess the impact of this symptom on activities of daily living (16).

Effectiveness, delay of appearance and disappearance of effects, and reinjection

All these studies reported an improvement in stump hyperhidrosis, with a significant statistically decrease in sweating versus placebo (12). However, this improvement was rarely complete in published studies, and estimated by patients at between 50 and 80% (12). The absence of complete improvement would be related to the inability to treat the entire amputation stump (17).
Improvement assessment was subjective and self-reported in most studies. The only randomized controlled trial used an objective technique, gravimetric analysis, which consists of weighing an absorbent paper inserted between the skin and the prosthesis and which will be weighed after exercise on a treadmill (12). Another objective method of evaluation was Minor's test with iodine and starch, which showed the disappearance of the sweat reaction with these products after injection (17). The botulinum toxin started giving effects from the 3rd day after injection (8). The medical check-up 3 weeks after defined the result (10,11). And this effect could persist for up to 12 months (8). The improvement was made both in terms of dermatological problems and better use to the prosthesis(12).

No studies have investigated the effects of reinjection of botulinum toxin in hyperhidrosis of the stump, but nevertheless this effect has been studied in axillary hyperhidrosis. A better result that lasts over time would be associated with an increasing number of injections (5,18).

Toxin type/dose

Only botulinum toxin type A marketed under the name Botox® has obtained marketing authorization in the symptomatic treatment of hyperhidrosis. Moreover, it is the one most used in the literature (7,8,11,13,15,17,19,20). However, some studies have used type B toxin (10,12,21). The use of serotype B would provide better dissemination and faster onset of results (10).
The dose of botulinum toxin type A injected varied between 100 and 300 units. A higher dose (500 units) was used for femoral amputations (11).

Injection techniques

Almost all injections in the literature have been made intradermally. A study compared between intradermal and intraepidermal injections, and showed better tolerance of the superficial technique but better effectiveness of the deep technique (20). The product would diffuse even if injected intramuscularly (19).

Identification of injection sites / number of injection's points

The number of injection points was on average between 20 and 50 points, and could even go up to 200 points in the literature (17).
The identification of the zones was different according to the teams. Some identified the points using Minor's iodine and starch test (7,7,10,13), and others performed a grid with injections distributed over the entire amputation stump (11, 12.15). In femoral amputations, only the lower two thirds of the stump were treated (11). Injection site did not affect botulinum toxin outcome (10). Extent of botulinum toxin type A diffusion may help to explain this.

Side effect/accident/local anesthesia/pain

No patient reported side effects in our series. In the literature, incidents are rare and often minor and reversible. The most frequent are hematoma at the injection site, dry mouth, feeling of muscle weakness or generalized asthenia (5,10,22,23). These effects are dose related.
In our study, the pain caused by the act was on average 5.17/10 on the visual analogue scale. Several authors have considered that local anesthesia was not necessary (10). Some authors have used lidocaine-based local anesthetics (11,12). And others have shown that with finer needles (0.3mm diameter, 27G), the injection was less painful (24). Other pain prevention techniques

such as nerve block anesthesia, use of nitrous oxide or hypnosis have been proposed in the literature (5).
However, all patients reported that despite the pain of the injection, it would not prevent them from getting tread again with botulinum toxin(12).

Conclusion

Intradermal injections of botulinum toxin in the symptomatic treatment of stump hyperhidrosis are effective and have few adverse effects. It improves the quality of life of our patients thanks to a better tolerance of the prosthesis. However, larger studies are needed to properly study the results.

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