Residual limb hyperhidrosis: use of botulinum-A toxin to improve prosthesis fit and function

Prosthesis satisfaction rates in patients with lower limb amputation have been reported to be as low as 43% (Dillingham et al, 2001). Follow-up studies of prosthesis-related complications have consistently demonstrated hyperhidrosis and subsequent complications as a common complaint among amputees. This paper presents four cases of traumatic bilateral lower limb amputees where botulinum toxin serotype A (BTX-A) was used to control residual limb hyperhidrosis. The patients were all satisfied with their reduction in residual limb sweating and expressed interest in obtaining future BTX-A treatment.

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KEY WORDS
Nurse education
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Follow-up studies of prosthesis-related complications and reported satisfaction rates have consistently demonstrated hyperhidrosis as a common feature among amputees (Dillingham et al, 2001; Davidson, 2002; Meulenbelt et al, 2009).

Hyperhidrosis, defined as excessive sudomotor activity of unknown pathogenesis and subsequent high levels of sweat production (Vorkamp et al, 2010), produces an unfavourable environment within the prosthesis socket. Mechanical stressors, occlusive dressings, poor fitting and macerated skin within the prosthesis socket frequently give rise to dermatological complications, serious discomfort and increased morbidity (Meulenbelt, 2007; 2009). Reported prosthesis satisfaction rates are as low as 43% in lower limb amputees (Dillingham et al, 2001), highlighting the shortcomings in clinical follow-up and treatment.

Mechanical stressors, occlusive dressings, poor fitting and macerated skin within the prosthesis socket frequently give rise to the development of dermatological complications, serious discomfort and increased morbidity.

Used in the treatment of hyperhidrotic disorders of various locations, namely the palms, feet, axilla, mouth and face (Frey's syndrome), botulinum toxin serotype A (BTX-A) has recently been used in the treatment of residual limb hyperhidrosis in complication-prone patients (Wollina et al, 2000). Patients with a history of recurrent skin degradation were selected for treatment, with hyperhidrosis being deemed the central provocative factor (Wollina et al, 2000).

Available treatments include topical antiperspirants (aluminium chloride), anticholinergics, iontophoresis, and surgical destruction of the sympathetic innervation and/or associated sweat glands (Vorkamp et al, 2010).

Standard treatment regimens, namely topical antiperspirant applied weekly, are largely ineffective or infrequently used with more than half of upper limb amputees reporting sweating levels within prosthesis as 'unacceptable' (Davidson, 2002).

In four male bilateral lower limb amputee British military personnel, the authors explored the use of BTX-A as an effective early treatment of residual limb hyperhidrosis.

Methods

A consecutive case series of four bilateral traumatic lower limb amputees (*Table 1*) was used to access the effectiveness of BTX-A in treatment of residual limb hyperhidrosis.

Patients were treated at University Hospitals Birmingham NHS Foundation Trust while undergoing stump revisions. Two vials (200 U; 100U per stump) of reconstituted BTX-A (Botox, Allergan, Inc, Irvine, CA) diluted with 8.0mL 0.9% sterile physiologic saline (100 U/4.0mL)

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Table 1
Patient demographics (adapted from BTX-A treatment of residual limb hyperhidrosis, Charrow et al, 2008)

Patient	Age (year)	Sex	Level of amputation, left lower limb	Level of amputation, right lower limb	Time since amputation (months)	Total dose (U)
1	26	Male	Transfemoral	Transfemoral	20	300
2	27	Male	Transfemoral	Transfemoral	4	200
3	22	Male	Transtibial	Transfemoral	28	200
4	24	Male	Transtibial	Transtibial	6	200

were injected intracutaneously in 0.1mL aliquots. Injections were made in a 1cm square grid pattern on distal stumps while patients were under general anaesthesia. Clinical follow-up and retrospective 9-question 7-Point Likert scale survey was used to assess the efficiency of hyperhidrosis treatment.

A clinical audit questionnaire was distributed to the study participants via the post. The questionnaire consisted of a 7-Point Likert scale, where 1 = 'strongly disagree', 4 = 'neither agree nor disagree', and 7 = 'strongly agree'. Nine retrospective questions were used to identify the effect that BTX-A had on residual limb hyperhidrosis, functional prosthetic use, dermatological complications and phantom or residual limb pain.

Results

In accordance with previous case reports (Wollina et al, 2000; Kern et al, 2004; Garcia-Morales et al, 2007; Charrow, et al, 2008), BTX-A treatment found patients very satisfied with their reduction in residual limb sweating, along with improved prosthesis use and functioning, and reduced skin irritation (*Table 2*). BTX-A was found to have no effect on phantom or residual limb pain. During clinical follow-up, patients expressed interest in obtaining future BTX-A treatment.

Discussion

Hyperhidrosis is a serious contributor to morbidity experienced by amputees, and is reported as the number one complaint in both lower (Meulenbelt et al, 2009) and upper limb (Davidson, 2002) amputee patients.

The hyperhidrotic state within prosthesis sockets contributes to a damaged skin barrier and poor prosthesis fitting which, in conjunction with mechanical stressors, promotes frequent dermatological complications such as pain as a result of skin degradation, pressure ulcers and bacterial infection (Meulenbelt et al, 2007). A survey of 805 lower limb amputees (42% due to trauma) found 63% experienced one or more skin complications in the month preceding the survey. One quarter found these complications to reduce their prosthesis use (Meulenbelt et al, 2009). The most commonly reported skin problems included pressure ulcers, skin infection, open wounds, and eczema (Meulenbelt et al, 2009).

A systemic review of lower limb amputees found that acroangiodermatitis, allergic contact dermatitis, bullous diseases, epidermal hyperplasia and malignant transformation (Marjolin's ulcer) have also been reported (Meulenbelt et al, 2007). Patients one and two in this series presented initially with bilateral skin degradation and infection, which prompted investigation into alternative therapies.

Table 2
Retrospective response to BTX-A effectiveness (SD=standard deviation) (Charrow et al, 2008)

Clinical measure	Patient response
Level of residual limb sweating decreased	6.25 +/- SD 0.5
Level of residual limb sweating within prosthesis decreased	6.75 +/- SD 0.5
Daily time spent in prosthesis increased	6.5 +/- SD 0.577
Achievable walking distance increased	6.25 +/- SE 0.5
General fit of prosthesis was improved	5.5 +/- SE 0.577
General functioning of prosthesis was improved	5.75 +/- SD 0.5
Level of experience of phantom limb pain decreased	1.5 +/- SD 0.577
Level of experience of residual limb pain decreased	1.5 +/- SD 0.577
Experience of skin irritation at site of prosthesis fitting decreased	6 +/-SD 0.0

Previous non-surgical treatment options for hyperhidrosis include topical antiperspirants, iontophoresis, and anticholinergics. Topical antiperspirants are an effective treatment for mild to moderate hyperhidrosis but require weekly application and can be associated with skin irritation and fabric damage (Charles, 2004; Vorkamp et al, 2010). Likewise, iontophoresis is time-consuming and may provoke skin irritation and blistering (Bhidayasiri and Truong, 2005; Vorkamp, et al, 2010). Anticholinergics are effective in treating hyperhidrosis but are significantly limited by systemic anticholinergic activity causing side-effects such as mydrisasis, glaucoma, drowsiness, urinary retention, and constipation (Vorkamp et al, 2010).

Surgical intervention for the treatment of hyperhidrosis is reserved for severe cases unresponsive to topical or non-invasive therapies. Endoscopic thoracic sympathectomy (ETS) is the preferred method, as well as surgical excision and subcutaneous liposuction, which have all proven effective. ETS provides long-term symptomatic relief but can be associated with severe complications, the most significant being compensatory hyperhidrosis at rates as high as 86% (Vorkamp et al, 2010). Other serious complications include intra-operative pneumothorax, brachial plexus injuries, Horner's syndrome, and damage to the great vessels (Bhidayasiri and Truong, 2005; Vorkamp et al, 2010).

BTX-A is a potent neurotoxin first developed as a treatment for muscular disorders including focal dystonias and muscular spasticity (Bhidayasiri and Truong, 2005). It is now available for the treatment of a myriad number of clinical conditions, including a number of hypersecretory and pathological pain disorders (Charles, 2004; Bhidayasiri and Truong, 2005). Its main pharmacological pathway inhibits the pre-synaptic release of acetylcholine, thereby preventing muscular contraction or other cholinergic dependent responses (Wenzel, 2004). Axonal sprouting from the blocked nerve terminals, along with molecular turnover will begin to restore function to affected muscle and/or gland at approximately three months (Wenzel, 2004; Bhidayasiri and Truong, 2005). A study assessing the dose efficiency of BTX-A in patients experiencing axillary hyperhidrosis found effective treatment lasting on average 4–9 months (Heckmann and Plewig, 2005), although reports of effects up to 18 months have been recorded (Lowe et al, 2003). It also concluded that doses of 100 U and 200 U of BTX-A are equally safe and effective, advocating the use of 100 U as more appropriate (Lowe et al, 2003). Adverse effects that can be associated with intracutaneous BTX-A therapy include local muscle weakness, pain at injection site and local haematoma formation (Naumann, et al, 1998; Bhidayasiri and Truong, 2005).

With regards to hyperhidrosis, current literature fails to emphasise the differences between traumatic amputations and those related to diabetes and peripheral vascular diseases.

As BTX-A is only a symptomatic treatment, repeated administration is the only option for control of chronic hyperhidrosis. The implications of this are important when considering the immunogenicity of BTX-A. The production of neutralising antibodies by the body's immune system reduces the effectiveness and longevity of BTX-A treatment (Wenzel, 2004). It is therefore important to use minimal dosing loads to prevent or delay the development of neutralising antibodies, reducing the frequency of therapy and increasing patient quality of life. Identifying specific areas of hyperhidrosis using Minor's iodine starch test (Vorkamp et al, 2010) and injecting points of hyperhidrotic activity in comparison to a grid pattern injection technique will reduce total dose (Garcia-Morales et al, 2007; Charrow et al, 2008). A previous case report found sweat draining from the upper thigh into the prosthesis socket, due to gravity reducing the dosing interval of BTX-A therapy. Subsequent infiltration of the thigh was successful in prolonging the asymptomatic period (Garcia-Morales et al, 2007). The substitution of alternative botulinum toxin serotypes was theorised as a potential method for preventing BTX-A immunogenicity. However, this has been disproven in recent studies which found cross-reactivity of antibodies between botulinum toxin A and B serotypes (Wenzel, 2004).

The use of BTX-A in the effective treatment of residual limb hyperhidrosis has been reported in four case studies involving a total of 14 patients with unilateral amputations, both upper and lower limb (Wollina et al, 2000; Kern et al, 2004; Garcia-Morales et al, 2007; Charrow, et al, 2008). Of these, only 10 patients (Wollina et al, 2000; Garcia-Morales et al, 2007; Charrow et al, 2008) were treated with intracutaneous injections, as directed by manufacturers for the treatment of axillary hyperhidrosis (Anderson, 2004; Charles, 2004). BTX-A was also reported to reduce phantom and residual limb pain in four patients using intramuscular injections (Kern et al, 2004). However, a following case report, in conjunction with this study, injecting intracutaneously failed to illicit the same effect (Charrow et al, 2008). This discrepancy is possibly due to the difference in injection techniques.

With reference to the study population, hyperhidrosis experienced by bilateral in comparison to unilateral amputees is likely to be more pronounced, reinforcing previous demonstrations of BTX-A's effectiveness. This phenomenon is a result of greater reduction in surface area available for evaporation and subsequent heat dissipation (Charrow et al, 2008). Further investigation involving intramuscular BTX-A injections for phantom and residual limb pain, as well as quantitative sweat measurements between unilateral and bilateral amputees using gravimetry is warranted (Vorkamp et al, 2010).

With regards to hyperhidrosis, current literature fails to emphasise the differences between traumatic

amputations and those related to diabetes and peripheral vascular disease (PVD) and the subsequent physiological and social discrepancies between the two populations.

The differences are important when targeting therapies and preventative measures at appropriate patients and meeting their expectations of prosthesis function. For example, patients whose amputation is associated with diabetes and PVD are generally older, accounting for 94% of elderly amputees (Rommers et al, 1997), and have lower reported rates of dermatological complications (Meulenbelt et al, 2009). This is most likely multifactorial, as a result of the underlying physiology of both diseases as well as the advanced age of the patient population. This results in reduced level of activity, lower basal sweat output, and compensatory alterations in skin density on the distal stump(s).

In the case of traumatic amputees, the population is younger and there are higher complication rates. This has been attributed to these patients walking longer distances, the length of time spent in prosthesis and patterns of prosthesis use — younger patients also often have higher activity levels and expectations of prosthesis function. However, a wide range of confounding factors such as smoking and information bias makes the conclusive assessment of these provocative variables difficult. Statistical analysis of the provocative and preventative determinates of residual limb skin complications is still highly ambiguous and requires further examination (Meulenbelt et al, 2009).

Conclusion

Hyperhidrosis is a commonly reported feature in amputee patients which lessens their prosthesis use, reducing patient independence and quality of life. Currently available treatment regimens are ineffective or associated with unacceptable adverse effects, such as chronic irritation and recurrent infection. BTX-A has been shown to be an effective alternative therapy in the treatment of residual limb hyperhidrosis in a number of open-label reports. A randomised double-blind control trial with a larger population base is warranted to determine the effectiveness of BTX-A in the treatment of residual limb hyperhidrosis. WUK

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Key points

- Hyperhidrosis is the most commonly received complaint from prosthesis-wearing amputees.
- Hyperhidrosis and associated skin complications reduce prosthesis use and patient quality of life.
- Current treatment regimens are largely ineffective and time-consuming.
- Botulinum toxin serotype A is effective and safe in long-term control of residual limb hyperhidrosis.

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