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CLINICAL REPORT

Botulinum Toxin Type A and B Improve Quality of Life in Patients with Axillary and Palmar Hyperhidrosis

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Hyperhidrosis is a common disorder that may have a severe impact on quality of life. The aim of this study was to investigate the clinical effect of two novel botulinum toxins, Xeomin®, a type A botulinum toxin, and Neurobloc®, a type B botulinum toxin, in the treatment of axillary and palmar hyperhidrosis. A total of 84 patients, 58 with axillary and 26 with palmar hyperhidrosis, were included in this open study. Axillae were injected with 107 ± 22 U Xeomin® and palms were injected with 213 ± 19 U Xeomin® and 264 ± 60 U Neurobloc® over the thenar eminences to avoid muscle weakness. At follow-up 3 weeks post-treatment, all patients treated for axillary hyperhidrosis reported satisfaction in self-ranking, evaporation decreased >40%, and Dermatology Life Quality Index (DLQI) score improved from 12.0 to 1.7 ($p < 0.05$). In the palmar group 95% were satisfied, evaporation decreased >50% and DLQI score improved from 10.3 to 1.2 ($p < 0.05$). Only one patient in the palmar group experienced muscle weakness. In conclusion, Xeomin® has an excellent effect on axillary hyperhidrosis and in combination with Neurobloc® on palmar hyperhidrosis. Neurobloc® may be an option for use in the treatment of palmar hyperhidrosis in order to minimize muscular side-effects. ***Key words: hyperhidrosis; botulinum toxin; life quality; DLQI; Xeomin; Neurobloc.***

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Hyperhidrosis is a condition that involves excessive sweating, and has a negative impact on quality of life QoL) (1). Up to 2.8% of the US population are affected by hyperhidrosis, which is mainly of the primary type (2). Primary hyperhidrosis can be focal, generalized or a combination of both. It has a strong genetic component (3, 4). Focal sweating affecting the hands, feet or axillae is controlled by the limbic system and frontal cortex. Generalized hyperhidrosis, on the other hand, is thermoregulatory and thus controlled by the hypothalamus.

First-line treatment for primary focal hyperhidrosis is topical aluminium chloride. When aluminium chloride is insufficient or causes intolerable side-effects, botulinum toxin (Btx), administered through intracutaneous micro-injections, is often used as a second-line treatment, although ionthophoresis may be an alternative (5). Compared with sympatectomy, Btx is effective and does not cause major side-effects (6–9) but has to be repeated for sustained activity. The mechanism of action of Btx includes cleavage of proteins that are important for acetylcholine release; Btx type A and B cleave SNARE proteins SNAP-25 and VAMP, respectively (10). Type B toxin (Neurobloc® in the EU; Myobloc® in the US) has less effect on spastic muscular disorders than does type A toxins (Xeomin®, Botox® and Dysport®), with a ratio of approximately 1:50 to 1:100 in favour of type A toxin (11). This is advantageous when treating areas of hyperhidrosis above small muscles, in order to avoid muscle weakness leading to impaired hand grip function (11, 12).

Repeated injections with short-interval and large-dose Btx may lead to immunoresistance (13). The proposed advantage of treatment with Xeomin®, a new type A toxin, is the low neuroprotein load, which is thought to correlate with a decreased risk of immunoresistence. Xeomin® was approved by European Medicines Agency in 2007 for the indications blepharospasm and spasmodic torticollis. The product contains only the 150 kDa dichain and none of the covering proteins that are present in other commercially available toxins (14). The removal of these proteins is said to minimize the immunostimulating properties of the preparation (15).

The aim of this study was to evaluate the clinical effect of Xeomin® and Neurobloc® on palmar hyperhidrosis, and of Xeomin® alone on axillary hyperhidrosis, with respect to QoL, self-ranking, evaporimetric measurements and side-effects.

MATERIALS AND METHODS

A total of 84 patients with primary focal hyperhidrosis, 58 with axillary hyperhidrosis and 26 with palmar hyperhidrosis, visiting the hyperhidrosis centre at Sophiahemmet, Stockholm, during the period 1 September to 15 November 2009, were consecutively included in this study. Exclusion criteria were bromhidrosis, neuromuscular disease, secondary hyperhidrosis, pregnancy or lactation in female patients, and previous treatment with Btx. Treatment with aluminium chloride failed in 52 (91.2%) of the patients with axillary hyperhidrosis and in 24 (92.3%) of those with palmar hyperhidrosis. Six patients with axillary hyperhidrosis and 2 with palmar hyperhidrosis

Table I. *Characteristics of the study population. Note the difference in age of onset of palmar and axillar hyperhidrosis; axillar hyperhidrosis appears to be dependent on sexual hormones, whereas palmar hyperhidrosis is not*

Characteristic data	Axillary ($n=58$)	Palmar ($n=26$)
Age, years, mean ± SD	32.3 ± 10.4	26.8 ± 10.2
Age at onset, years, mean ± SD	17.0 ± 7.5	9.9 ± 6.3
Heredity, *n* (%)	27 (46.6)	10 (38.5)
Most triggering factor, *n* (%)		
Stress	33 (56.9)	12 (46.2)
Exercise/heat	18 (31.0)	12 (46.2)
Cold	2 (3.4)	0
None	5 (8.6)	2 (7.6)
DLQI, mean ± SD	12.0 ± 5.5	10.3 ± 7.0

DLQI: Dermatology Life Quality Index; SD: standard deviation.

had no previous treatment. The patients' characteristics are shown in Table I.

Injection procedure

Intracutaneous injections of the axillae were performed in a square pattern with 12 mm between injections using 2 U Xeomin® (Merz Pharmaceuticals, Frankfurt, Germany), 20 U/ml, per injection over the whole hyperhidrotic area. The mean ± SD dose for both axillae was 107 ± 22 U. Palms were injected in a square pattern, with 15 mm between injections, using 1.5 U Xeomin®, 20 U/ml, per injection. The mean ± SD dose for both palms was 213 ± 19 U. Over the thenar eminences, injections every 12 mm with 7.5 U Neurobloc® (Eisai Europe Ltd, Hatfield, UK), 250 U/ml, per injection was used. The mean ± SD dose for both sides was 264 ± 60 U. Injections were performed with a 0.3 ml syringe and a 0.33 × 12 mm needle (Omnican, Braun, Belgium).

Treatment of axillary skin was usually performed without anaesthesia, but 2 patients received topical aneasthesia, EMLA® (AstraZeneca, Södertälje, Sweden), 60 min before injections. Twenty-five patients treated on the palms received regional anaesthesia of the ulnar and median nerves at the wrist, 5 ml Carbocain®, 10 mg/ml (AstraZeneca) at each nerve. One patient received intravenous regional anaesthesia using low torniquets and Citanest® (AstraZeneca) 0.5%, 0.8 ml/kg (16).

Methods

Patients completed the Swedish translation of the Dermatology Life Quality Index (DLQI) questionnaire before treatment and at the follow-up visit 25 ± 8 days after treatment. Each question (total 10 questions) of the DLQI is graded 0–3, covering 6 domains of QoL. Unanswered questions are scored 0. The total DLQI score can be interpreted in terms of the effect the dermatological condition has on the patients' QoL according to: 0–1 no effect at all, 2–5 small effect, 6–10 moderate effect, 11–20 very large effect, and 21–30 extremely large effect (17).

Since evaporation correlates with the amount of sweat produced, evaporimetric measurements were performed before and after treatment. The VapoMeter (Delfin Technologies Ltd, Kuopio, Finland) is a hand-held, non-invasive, closed-chamber device that measures transepidermal water loss (18). Measurements were performed at room temperature in a calm, air-conditioned room. The VapoMeter was held gently against the skin until a steady-state value was obtained for at least 15 s. The evaporation rate is expressed in g/m^2h.

At the follow-up visit patients were asked to write down all possible side-effects following treatment and to rank the treatment result according to: 1 (no effect), 2 (small effect), 3 (moderate effect), 4 (satisfied but not completely dry) or 5 (satisfied and completely dry). The duration of treatment effect was estimated as the time from Btx injections to the subsequent treatment of the same hyperhidrotic area. Renewed treatment was not allowed earlier than 3 months after the first treatment due to the risk of immunization. If a patient experienced an effect shorter than 3 months this was registered in the study protocol. Patients who did not receive a second treatment were contacted by telephone and asked to estimate the effect duration. They were also asked if they would consider another treatment with Btx.

The study was approved by the local ethics committee, and written informed consent was obtained from all patients.

Statistical analyses

Sign tests were used to test the null hypothesis that there is no difference in DLQI scores before and after Xeomin® and Neurobloc® treatment of axillary and palmar hyperhidrosis. *p*-values ≤ 0.05 were considered statistically significant.

Variables were described as mean values ± SD or median values (25^{th}–75^{th} percentiles) and frequencies.

RESULTS

All patients treated for palmar hyperhidrosis were satisfied with the treatment, ranking it as 4 or 5. Fifty-five of 58 (95%) of the patients treated for axillary hyperhidrosis were satisfied with the treatment, while 2 patients reported moderate effect (ranking 3) and 1 patient reported a small effect (ranking 2). After receiving a second treatment with Neurobloc® (375 U per axilla) or Dysport® (200 U per axilla, Ipsen Pharmaceuticals), 2 of the unsatisfied patients ranked the treatment result as 4 or 5 (satisfied). One patient was still not satisfied after a second treatment and was referred to a plastic surgeon for excision of axillary tissue.

Sign tests showed that the QoL in axillary and palmar hyperhidrosis was significantly improved following treatment with Xeomin® and Xeomin®/Neurobloc® ($p < 0.05$ in both groups). All patients, except for 3, experienced improved QoL. No patient had a negative trend in DLQI before and after treatment; however, one patient in the axillary group and two in the palmar group had the same value before and after treatment.

Forty-five percent of the patients treated for axillary hyperhidrosis and 42% of those treated for palmar hyperhidrosis achieved a DLQI score of 0 after treatment. Including all patients, the mean ± SD DLQI score improved from 12.0 ± 5.5 to 1.7 ± 2.6 ($p < 0.05$) in patients with axillary hyperhidrosis, and from 10.3 ± 7.0 to 1.2 ± 1.5 ($p < 0.05$) in patients with palmar hyperhidrosis. In both groups questions 2 (embarrassment and self-consciousness), 5 (social and leisure activities), 7 (working, studying) and 8 (problems with partner, close friends, relatives) generated high mean scores, and patients with axillary hyperhidrosis also reported high scores on question 4 (clothing) (Table SI; available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1464).

Forty-eight of 58 (83%) patients with axillary hyperhidrosis and 18 of 26 (70%) patients with palmar hyperhidrosis underwent evaporimetric measurements. The drop out was random and due to local practical circumstances. On a group basis the evaporation rates were reduced >50% in the axillary skin area and >40% in the palmar skin area post-treatment. The results are shown in Fig. 1.

All side-effects in this study were mild and transient (Table II). In total, 58% of subjects reported any possible side-effect in the palmar group, with "dry palms" being the most common. The dryness was most prominent in the first 2 weeks. Only one patient reported local muscle weakness in the palmar group. In the axillary group 21% of subjects experienced side-effects, with compensatory sweating being the most reported. Compensatory sweating was sometimes obvious, but in other patients sweating from non-treated parts could be a feasible explanation. In total, only 1 of 84 patients experienced a systemic side-effect, of dry mouth. The duration of treatment effect was defined as the time from Btx injections to next treatment of the same location. However, if the treatment effect lasted < 3 months this was reported by the patient at the time of relapse treatment and registered in the case report form. When the study was finalized, 51/58 of the patients treated for axillary hyperhidrosis and 23/26 of the patients treated for palmar hyperhidrosis chose a second treatment. Patients treated for axillary hyperhidrosis reported a median (25^{th}–75^{th} percentile) effect duration of 4.9 (4.0–7.8) months, whereas the median duration of palmar treatment was 5.3 (4.2–6.6) months. At the time of the second treatment, 48% and 42% of the patients treated for axillary and palmar hyperhidrosis, respectively, reported an on-going but unsatisfactory effect of the first treatment.

The patients who did not receive a second treatment with Btx, were all telephoned and asked to report the duration of the treatment effect. Including the answers from these patients, a median effect duration of 4.9 (3.8–8.0) months for axillary hyperhidrosis and 5.2 (4.2–6.9) months for palmar hyperhidrosis were calculated. In the telephone interview, 2 patients with axillary hyperhidrosis reported an on-going effect 19 months after treatment. Eight of 10 patients interviewed by telephone would consider further treatments, but one patient receiving axillary injections with topical anaesthesia found the injections too painful and another patient, receiving axillary injections without anaesthesia, declined injections due to short duration of effect.

Table II. *Possible side-effects reported in the study. In the palmar group, dryness dominates, and in both groups approximately 10% of patients experienced compensatory sweating (*n = *58)*

Side-effect	Axillary *n* (%)	Palmar *n* (%)
Any side-effect	12 (20.7)	15 (57.7)
Bruises[a]	0	1 (3.8)
Compensatory sweating	5 (8.6)	3 (11.5)
Tenderness, pruritus, swollen[a]	4 (6.9)	4 (14.8)
Warm skin[a]	2 (3.4)	0
Dry mouth	1 (1.7)	0
Dryness of skin	0	6 (23.1)
Muscle weakness	0	1 (3.8)

[a]At the site of injection.

DISCUSSION

This open-label study clearly shows that Xeomin® alone and in combination with Neurobloc® abolish sweating in patients with axillary and palmar hyperhidrosis. Patients' own evaluation (100% with palmar and 95% with axillary hyperhidrosis were satisfied) and gravimetric measurement (> 40% reduced evaporation) was accompanied by a significant improvement in QoL. The main results of our study are consistent with other studies performed in axillary and palmar hyperhidrosis treated with Botox® and Dysport® (8, 19, 20).

When analysing the gravimetric results before and after treatment in our study, responders have been defined as patients with ≥ 50% reduction of sweat production compared with baseline values (21). On a group basis, this was achieved among patients with axillary hyperhidrosis, and almost accomplished in

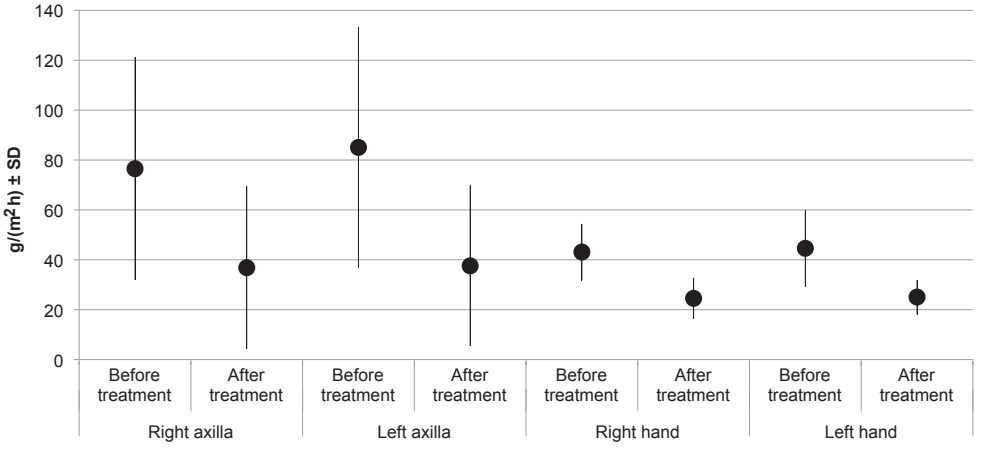

Fig. 1. Results of evaporimetric measurements. On a group basis, evaporimetric measurement is valid, with no side difference (right/left) and a substantial improvement (> 50% in palmar and > 40% in axillar hyperhidrotics) 3 weeks after botulinum toxin treatment. The higher values and more spread (SD) in the axillary group may be explained by the more wrinkled skin compared with the volar location.

patients with palmar hyperhidrosis. However, the use of laboratory equipment for assessing sweating has been questioned and perceived as too time-consuming and not sufficiently validated (22). Evaporimetric measurements are believed to underestimate the pre-treatment sweating because not all sweat evaporates if the skin area is dripping with sweat.

Therefore it is more appropriate to monitor a change in QoL with validated tools, such as the DLQI, since the effect on patients' daily life is more important than gravimetric and planimetric data. DLQI scores > 10 are considered a severe negative influence on QoL (17). For instance, a total DLQI score of > 10 is a major criteria when considering biological medications in psoriasis treatment (23). In our study, as well as in other studies on hyperhidrosis (8, 19, 20), the pre-treatment total score of the DLQI exceeds 10, suggesting that hyperhidrosis is a severe handicap affecting QoL in a similar way to severe skin diseases. Injections with Xeomin® alone and in combination with Neurobloc® dramatically reduced the DLQI score in patients with axillary and palmar hyperhidrosis in our study. Non-treated hyperhidrotic areas of the skin, compensatory sweating or other concomitant skin diseases may explain why no more than 42–45% of the study population achieved a total DLQI score of zero after treatment. It is important to examine all hyperhidrotic areas when a patient presents with hyperhidrosis. In fact, the majority of patients in our study reported extreme sweating from several skin locations. Treatment studies addressing the need to treat several areas of the skin are required.

Xeomin® was introduced as a novel Btx type A with a lower risk of immunoresistance. Compared with Botox® (5 ng/100 U) and Dysport® (0.9 ng/100 U), Xeomin® (0.6 ng/100 U) contains less neurotoxin protein. This factor may be important when treating chronic diseases, such as hyperhidrosis, which must be treated 1–4 times annually over a period of decades. Side-effects in the study were local, mild and transient, which is consistent with other studies on the use of Btx for treatment of palmar hyperhidrosis (6, 8, 9). Only one patient was affected by a systemic side-effect (dry mouth). Since the covering proteins are removed from the 150 kDa dichain in Xeomin® it is comparably small in size. Thus, the possibilities of Xeomin giving rise to increased spread from the injection site and systemic side-effects have been discussed. The covering proteins have, however, been shown to dissociate rapidly after injection, leading to identical Btx size, and consequently similar diffusion rate, for different formulations (24).

Neurobloc® was injected over the thenar emininence in order to avoid muscle weakness, as type B toxin appears to have a relatively low effect on α-motor neurones to muscles compared with sudomotor nerves (25, 26). Data from healthy volunteers suggest a similar effect of A- and B-toxins on sudomotor nerves (25). Only one patient with palmar hyperhidrosis experienced muscle weakness in this study, which is a low figure compared with other studies using type A toxins over the thenar eminence (27). For this reason we consider Neurobloc® a first-line option for Btx treatment in palmar hyperhidrosis in patients who need to maintain a high level of hand muscle control, e.g. musicians.

The mean effect duration in palmar and axillary hyperhidrosis in our study was approximately 5 months. Interindividual variation was large, with 2 patients experiencing onoing effect after 19 months, which is consistent with other studies (6). The effect duration of Btx treatment may be defined in several ways. Dressler (28) defined effect duration as the time between Btx injection and the onset of returned sweating, as estimated by the patient. Others have defined effect duration as the time from injection to the point when the patient reaches a predetermined reduction in effect (29, 30). The current study focused on a clinical situation, and duration was defined as the time to next treatment of the same hyperhidrotic area. Other factors influencing the duration of effect might be the cost of a second treatment and the availability of treatment. In our study, the patients were provided with relapse treatment on-demand, which may be the reason why almost half of the patients had an on-going, but not sufficient, effect. Due to the variation in definitions of effect duration it is difficult to compare results from different studies.

In conclusion, Xeomin® has an excellent effect in axillary hyperhidrosis and in combination with Neurobloc® in palmar hyperhidrosis, improving patients' QoL. Side-effects were mild, local and transient. Neurobloc® may be an option in the treatment of palmar hyperhidrosis, in order to minimize muscular side-effects.

Conflicts of interest: K. Rosell and K. Hymnelius declare no conflict of interest. Carl Swartling: shareholder in Hidroskliniken i Sverige AB.

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