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BRIEF REPORT

Botulinum Toxin A and B for Palmoplantar Hyperhidrosis

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ABSTRACT

Introduction: Hyperhidrosis is characterized by unpredictable, uncontrollable and excessive sweating. It occurs at rest and is not related to temperature. Hyperhidrosis is a common disorder that has a negative impact on quality of life (QoL). The aim of this quality assurance study was to investigate how treatment of palmoplantar hyperhidrosis with botulinum toxin A (BTX-A) and botulinum toxin B (BTX-B) led to improvement of patient reported outcome measures related to QoL.

Methods: A total of 35 patients with palmar and/or plantar hyperhidrosis who had received BTX-A (Dysport®) and BTX-B (NeuroBloc®) for palmar hyperhidrosis and BTX-B for plantar hyperhidrosis were included in this study. In total, palms were injected with a median dose (low to high) of 400 (100–550) units BTX-A and a median dose (low to high) of 200 (200–500) units. BTX-B was used in the thenar and hypothenar areas to avoid muscle weakness. In the soles a total median dose (low to high) of 600 (475–1000) units BTX-B was injected.

Results: At follow-up 2 weeks post-treatment, patients' Dermatology Life Quality Index (DLQI) score improved from 13 to 2 ($p < 0.001$).

Conclusion: We found that BTX-A and BTX-B treatment for palmar hyperhidrosis and BTX-B treatment for plantar hyperhidrosis led to a substantial improvement of QoL.

Keywords: Botulinum toxin; Dysport®; NeuroBloc®; Palmoplantar hyperhidrosis

Key Summary Points

There are few studies investigating the effect of botulinum toxin B (BTX-B) in palmoplantar hyperhidrosis.

The purpose of this study was to investigate how treatment with botulinum toxin A (BTX-A) and BTX-B led to improvement of patient reported outcome measures related to quality of life (QoL).

This study showed that BTX-A and BTX-B treatment for palmar hyperhidrosis and BTX-B treatment for plantar hyperhidrosis led to a substantial improvement of QoL.

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INTRODUCTION

Hyperhidrosis is characterized by unpredictable, uncontrollable and excessive sweating. It occurs at rest and is not related to temperature. Most often it affects the axillae, palms and soles, but it may also involve the groin, face or any location of the body. Hyperhidrosis can be primary or secondary. Primary hyperhidrosis has no identifiable cause (1).

It is estimated that primary hyperhidrosis overall affects 4.8% of the US population (2) and palmar hyperhidrosis 0.6–1% (3). Hyperhidrosis can have a negative impact on quality of life (QoL) (4), and many experience anxiety and depression (5). It may impair occupational and daily activities owing to difficulties handling electronic equipment, pens and paper. Skin maceration and soreness can create functional problems. The condition is unpredictable and uncontrollable in nature, which can make it very distressing (1).

The treatment of palmoplantar hyperhidrosis includes topical aluminium chloride, iontophoresis, anticholinergic oral medications, botulinum toxin (BTX) and endoscopic thoracic sympathectomy (6). A systematic review concluded that there is little high-quality evidence supporting these interventions. However, there is some promising evidence for the effectiveness, but insufficient evidence on the effect on QoL, of BTX for palmar hyperhidrosis (1).

BTX is a strong neurotoxin produced by the gram-positive, anaerobic bacterium *Clostridium botulinum*. Seven serotypes (BTX-A, B, C, D, E, F and G) are known, of which BTX-A and BTX-B are available for commercial use (7). BTX works by inhibiting the exocytosis of acetylcholine from the presynaptic cell into the synaptic cleft. BTX-A and BTX-B has the same sudomotor effect, but BTX-A has a stronger effect on α-motor neurons and muscles than BTX-B with a ratio of 1:50–100 in favour of BTX-A (8, 9). In dermatology, BTX is used to treat disorders such as hyperhidrosis, acantholytic disorders and pruritic dermatoses, as well as for cosmetic purposes. BTX also has several non-dermatological indications (7, 10).

BTX-A in the treatment of palmar hyperhidrosis is reported to be associated with adverse effects such as decreased grip strength and muscle weakness (11, 12). The difference between BTX-A and BTX-B in effect on sweat glands versus muscles is thought to make BTX-B more suitable in the treatment of hyperhidrosis in areas above small muscles, to minimize the potential adverse effect of muscle weakness (13). Three studies have investigated the effects of BTX-B treatment on palmar hyperhidrosis, of which one combined BTX-A with BTX-B. All three studies found the treatment to be effective in reducing sweating, and muscle weakness was reported as significant in one study (13, 14, 15). The difference in effect on muscle weakness could be due to injection procedure or how adverse effects were investigated (15).

The Department of Dermatology, University Hospital of North Norway (UNN), started in 2016 treatment of primary palmoplantar hyperhidrosis with BTX. The purpose of this study was to investigate how treatment with BTX-A and BTX-B led to improvement of patient reported outcome measures related to QoL.

MATERIALS AND METHODS

Trial Overview and Population

This was a single-centre retrospective quality assurance study of treatment given in the outpatient clinic of the Department of Dermatology at the University Hospital of North Norway (UNN). The study was conducted in accordance with the Squire 2.0 criteria. We have consulted the local ethics committee (EC) and got confirmation that this project does not meet the federal definition of human subjects research requiring the review and oversight of an institutional review board, as this is a quality assurance project. Informed consent was obtained as part of standard care.

A total of 35 patients with palmar and/or plantar hyperhidrosis who had received BTX-A (Dysport®) and BTX-B (NeuroBloc®) for palmar hyperhidrosis and BTX-B for plantar hyperhidrosis were included in this study. The

treatment was given between years 2016 and 2023. Key exclusion criteria were current pregnancy and breastfeeding. Patients completed the Norwegian translation of the Dermatology Life Quality Index (DLQI) questionnaire at the clinic before treatment. They were instructed to complete the DLQI questionnaire once again at home 2 weeks after treatment whereupon they would send it by post to the clinic. The questionnaire has 10 questions, covering different domains of QoL. Summarizing the questionnaire gives a score between 0 and 30, which can be understood in terms of the effect hyperhidrosis has on the patients' QoL with the following bands: 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 (16).

Interventions

The abovementioned difference in effect on sweat glands versus muscles has made BTX-B standard intervention at UNN when treating hyperhidrosis in the soles of the feet and thenar and hypothenar areas of the palms.

BTX-A was diluted to 50 IU/ml and BTX-B was diluted to 25 units IU/ml in normal saline. Intradermal BTX micro-injections were spaced about 10–15 mm apart on affected areas, with 0.05 ml per micro-injection. Equally divided between the palms, a median dose (low to high) of 400 (100–550) units BTX-A was injected centrally in the palms, and a median dose (low to high) of 200 (200–500) units BTX-B was used in the thenar and hypothenar areas. Equally divided between the soles, a median dose (low to high) of 600 (475–1000) units BTX-B was injected. The total dose per treatment varied depending on the size of the patient's hands and soles and the size of the affected area, and in some cases a reduced dose due to insufficient anaesthesia was used.

Most patients find the injections painful, and 25 patients were given nerve blocks with mepivakain (Carbocain®), where one ampoule of 1.8 mg was diluted with a 5 ml solution NaCl. For plantar treatment, 2.5 ml of the solution was injected medially and laterally in each ankle. For palmar treatment, 1 ml was injected in the median nerve, 1 ml in the ulnar nerve and 0.5 ml on a branch of the radial nerve, per wrist. This gives a maximum total dose of 7.2 mg mepivakain if both palms and soles are treated. Three patients received general anaesthesia with alfentanil (Rapifen®) 1 mg or morphine 5 mg. Four patients were given a combination of nerve block and general anaesthesia, two patients did not receive any anaesthesia and one patient was cooled with ice-packs on the palms before treatment.

Trial Outcomes

The primary objective of this study was to present quality of life data in patients at baseline and 2 weeks after treatment. The outcome was improvement of DLQI at week 2 from baseline.

Statistical Methods

Baseline characteristics of the study participants were compared using descriptive statistics. Categorical variables were expressed as frequencies. Continuous variables were summarized using means with standard deviations or as medians with minimum and maximum values. The median differences in DLQI at baseline and 2 weeks, and 95% confidence intervals (CI) were estimated with the Hodges–Lehmann method. *p*-Values are from the Wilcoxon signed-rank test. DLQI changes were also explored using graphical presentation. Mann–Whitney *U*-test was used to evaluate differences between groups. The level of significance was set at $p = 0.05$. The statistical analyses were performed using IBM® SPSS® Statistics, version 28.0.1.0 (142).

RESULTS

The study population was made up of 26 women and 9 men with a young median age of 26 years. The median body mass index (BMI) was 26 kg/m^2, although data were missing for 11 participants. None were current smokers, although data were missing for 12 participants. To determine the disease duration, patient

medical records were reviewed. For some participants, only descriptive formulations were documented, and in these cases disease duration was categorized by estimation into groups of less than 10 years, 10 to 20 years, and more than 20 years (Table 1).

The primary outcome, DLQI, improved from a baseline median of 13 (maximum, 24; minimum, 5) to 2 (maximum, 8; minimum, 0) at 2 weeks ($p < 0{,}001$; Fig. 1). All patients experienced improved QoL, and nine patients reported no residual impairment of QoL (DLQI = 0). The estimated median improvement in DLQI was 11 (maximum, 24; minimum, 2) with a 95% confidence interval from 9 to 13.

Of the 35 participants in this study, 13 received treatment exclusively to the palms, 8 to palms and axillae, 6 to palms and soles, and 8 to various combinations of palms, soles, axillae, groin, head, chest and back (Table S1). The result for both the palmar and palmar plus plantar subgroups was an estimated median improvement in DLQI of 10.5, significant at the 5% level (Fig. 2). As only one patient was exclusively treated on the soles, results for this location was not analysed separately.

The median baseline DLQI for men and women were 10 and 14, respectively. The estimated median improvement in DLQI for men was 7 (CI 4.5–15; $p = 0.008$), and for women 12 (CI 9.5–14; $p < 0.001$). The difference in DLQI improvement between sexes was not statistically significant ($p = 0.119$).

Table 1 Participant baseline characteristics

Characteristics	*n* = 35
Sex (male, female; *n*)	9, 26
Mean age (low to high)	26 (15–52) years
Mean body mass index (low to high)	26 (17–34) kg/m^2
Data missing (*n*)	11
Current smoking status (yes/no) (*n*)	0/23
Data missing (*n*)	12
Family history of hyperhidrosis (yes/no; *n*)	19/4
Data missing (*n*)	12
Duration of hyperhidrosis (*n*)	
< 10	7
10–20	16
> 20	5
Data missing (*n*)	7
Previously treated with iontophoresis (yes/no) (*n*)	15/19
Data missing (*n*)	1
Previously treated with topical aluminium chloride (yes/no; *n*)	25/0
Data missing (*n*)	10
Previously treated with oral anticholinergic drugs (yes/no; *n*)	5/24
Data missing (*n*)	6
Previously treated with BTX on affected area (yes/no; *n*)	2/33

BTX botulinum toxin

DISCUSSION

In this study BTX-A and BTX-B treatment for palmar hyperhidrosis and BTX-B treatment for plantar hyperhidrosis significantly improved QoL for patients at 2 weeks from baseline. The participants had a baseline median DLQI of 13, which indicates that their hyperhidrosis had a very large effect on their life. At 2 weeks, the median DLQI was 2, which can be interpreted as a small effect on their life (16). One prospective clinical study of BTX-A and BTX-B combined for palmar hyperhidrosis found an improvement in DLQI from 10.3 to 1.2 at approximately 3 weeks' follow-up, which is consistent with our study (13). Two other studies that found BTX-B treatment of palmar hyperhidrosis to be effective have used outcome measures such as measured amount of sweating by iodine starch test, and palmar hyperhidrosis quality of life (P-HQOL) score, making these results not directly comparable even though the direction of the result is consistent with our study (14, 15). It

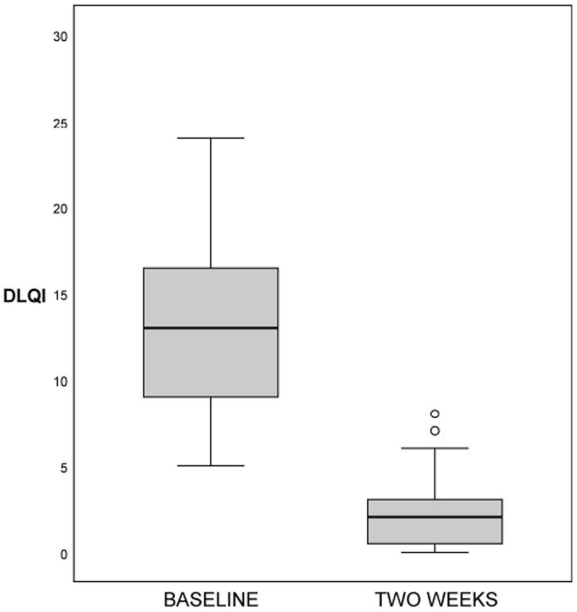

Fig. 1 DLQI at baseline and 2 weeks after treatment shown as a box-plot. Box limits represent the range of the central 50% of the data, medians are depicted as a horizontal solid line, whiskers represent maximum and minimum values and outliers are depicted as an open circle. *DLQI* Dermatology Life Quality Index

has been argued that it is more appropriate to measure the effect of an intervention with a validated QoL tool such as DLQI, as effects on a patient's life is the most important (13).

Minimal clinically important difference (MCID) has been defined as the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management (17). MCID is useful, as it connects the degree of patient-experienced change to treatment decisions in clinical practice; it emphasizes the importance of the patient perspective, and it is easily understood (18). One study recommended MCID for DLQI in skin diseases such as hyperhidrosis to be set to 4, and another study estimated MCID for palmar hyperhidrosis to be 3 (19, 20). For the participants in our study the median improvement in DLQI was 11. Hence, our study repeated clinically relevant improvement of BTX-treatment in palmoplantar hyperhidrosis.

Different dose regiments have been used in the studies of BTX-B in palmar hyperhidrosis. Rosell et al., as with our study, combined BTX-A and BTX-B with a mean dose of 213 IU BTX-A (Xeomin®) and a mean dose of 264 IU BTX-B (NeuroBloc®) for both palms. All side effects in the study were mild and transient, with dry palms in the first 2 weeks being the most prominent. Only 1 of 26 patients experienced muscle weakness (13). Basciani et al. used 5000 IU BTX-B (NeuroBloc®) for both palms. No serious adverse effects were reported, including no significant differences from baseline to follow-up in hand grip strength measurement (15). Baumann et al. used 5000 IU BTX-B (Myobloc®) for both palms. In contrast, this study found that the majority of patients had adverse effects such as dry mouth (90%), excessively dry hands (60%), indigestion/heartburn (60%), muscle weakness (60%) and decreased grip strength (50%) (14). It has been suggested that the unexpectedly high number of adverse effects may be attributed to the injection procedure and the methodology used to investigate side effects (15). In our study, a median dose of 400 IU BTX-A plus a median dose of 200 IU BTX-B was used for treating palmar hyperhidrosis and a median dose of 600 IU BTX-B for treating plantar hyperhidrosis. Adverse effects were not systematically recorded in our study. Fear and the experience of pain varies throughout the population. The procedure can be painful, and some patients express anxiety before the procedure. Therefore, some patients

	Palmar (n = 13)			Palmar and plantar (n = 6)		
	Est. median	CI (95%)	p value	Est. median	CI (95%)	p value
DLQI reduction	10,5	7,5-14	0,001	10,5	6,5-15,5	0,028

Fig. 2 Results from patients per exclusively treated locations. *DLQI* Dermatology Life Quality Index

were offered nerve block or general anaesthetics prior to treatment.

This study has several weaknesses such as lack of control group and a retrospective design. Due to the latter, there was no protocol during treatment, and data on characteristics such as body mass index, disease duration, smoking status, family history and previous treatment was unavailable for some participants. A total of 16 participants were simultaneously treated with BTX on at least one other location, potentially disturbing baseline and change in DLQI. Systematic recording of confounding hyperhidrosis treatment, such as iontophoresis, oral anticholinergic drugs and topical aluminium chloride, was not conducted. Still, review of patient journals did not reveal any examples of relevant concomitant treatment. The follow-up time was only 2 weeks, thus limiting our knowledge of the long-term effects of the treatment. However, in our clinical experience and comparing with similar studies examining the effect of BTX-B for palmar hyperhidrosis, we would expect the effects of the treatment to be significant reduction of sweating and improved QoL for 2–5 months (14, 15).

CONCLUSION

We found that BTX-A and BTX-B treatment for palmar hyperhidrosis and BTX-B treatment for plantar hyperhidrosis led to a substantial improvement of QoL. Our study is too small to conclude whether the effects on plantar or palmar hyperhidrosis are greater.

Author Contributions. All authors contributed to the study concept and design. Material preparation and data collection were performed by Trond Eilertsen and Bjørn Ø Kvammen. Analysis were performed by Trond Eilertsen. The first draft of the manuscript was written by Trond Eilertsen, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Trond Eilertsen, Bjørn Ø Kvammen, and Øystein Grimstad report no conflicts of interest.

Ethical Approval. Not applicable. We have consulted the local ethics committee (EC) and got confirmation that this project does not meet the federal definition of human subjects research requiring the review and oversight of an institutional review board, as this is a quality assurance project. Informed consent was obtained as part of standard care.

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