Low-Dose Efficacy of Botulinum Toxin A for Axillary Hyperhidrosis

A Randomized, Side-By-Side, Open-Label Study

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Objective: To compare 2 doses of botulinum toxin A in view of dose-dependent efficacy, longevity, and safety.

Design: Side-by-side, controlled, randomized clinical trial with extended follow-up over 2 treatment cycles. Patients were injected with 200 U of botulinum toxin A (Dysport; Ipsen Ltd, Wrexham, England) into one axilla and 100 U into the other axilla in a randomized fashion. After 48 weeks of follow-up, the patients were given a second treatment with identical doses to the respective axillae and were again followed up for 48 weeks. Gravimetric measurements of sweat production and the patients' own rating of sweating were monitored.

Setting: University-based outpatient clinic.

Patients: Forty-three subjects with primary axillary hyperhidrosis that was unresponsive to topical therapy.

Main Outcome Measure: Absolute values of sweat production.

Results: Two weeks after treatment, the sweat production was significantly reduced compared with baseline levels. Both doses were equally effective. At week 48, the sweat production had returned to baseline levels irrespective of the dose. After the second treatment, both doses were again equally effective at any follow-up point. At the end of the follow-up period (96 weeks) for the second treatment, the sweat production was significantly lower than at the end of the first follow-up period (48 weeks). The treatment was well tolerated, and there were no lasting or severe adverse effects.

Conclusions: Short- and long-term results show that doses of 100 and 200 U of botulinum toxin A are equally safe and effective. However, because of cost considerations and possible adverse effects, the lower dose is preferable for treating axillary hyperhidrosis.

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Primary axillary hyperhidrosis is an autonomic neuronal dysfunction that can result in uncontrollable, excessive sweating. Patients suffer from skin maceration, secondary microbial infections, drenching and ruining of clothes, and social stigmatization. Botulinum toxin A blocks the autonomic innervation of sweat glands and has therefore become a preferred treatment modality for severe axillary hyperhidrosis that is unresponsive to other established therapies, eg, topical application of aluminum chloride. Several double-blind, placebo-controlled, multicenter clinical trials have shown that botulinum toxin A is a safe and highly effective therapy with high patient satisfaction. However, most patients require more than 1 treatment over time, as sweating tends to recur after an average of 4 to 9 months. Also, botulinum toxin A treatments are more costly than topical applications of aluminum chloride and have to be administered intracutaneously, with precise placement and dosing of the drug. Thus, the necessity for optimizing botulinum toxin A treatment is evident. One approach to reduce treatment frequencies has been high-dose therapy. However, high-dose therapy has been criticized as potentially risking antibody induction against botulinum toxin A. So far, no controlled trials have been conducted to prove the hypothesis that high doses are truly more effective than lower doses.

The issue of finding the optimal dose is complicated by the fact that there are 2 distinct pharmaceutical preparations of botulinum toxin A: Botox (Allergan, Irvine, Calif) and Dysport (Ipsen Ltd, Wrexham, England). Both products are measured in mouse units, but the respective units appear to have different clinical potencies in humans. Consequently, clini-
Dysport, on the other hand, is packaged in vials of 500 U. It should be kept in mind, however, that 1 U of Dysport is not the same as 1 U of Botox. Early clinical trials with Dysport had been conducted with the same practical approach: 1 vial per patient. Thus, 1 vial of Dysport was split for both axillae, yielding 250 U per axilla. Later studies, however, applied less than 1 vial per patient, with no apparent loss in efficacy. When 200 U per axilla was compared side by side with 100 U in one study, there was no significant difference in safety or efficacy between the 2 doses with a follow-up period of 24 weeks. It could not be ruled out from that study, however, that long-term efficacy (>6 months) may be inferior with the lower dose, especially when treatments were to be repeated, resulting in lower cumulative doses over time. A dose-ranging study using Dysport in healthy volunteers for quantitative sweat evaporation measurements established a dose-dependent duration of the antiperspiring effect, which further focused the discussion on long-term dose efficacy.

The present study was carried out to address the issue of long-term efficacy and safety in a clinically relevant setting of axillary hyperhidrosis comparing 100 U with 200 U side by side over a 2-year follow-up period with side-matched reinjections.

The study protocol was approved by the ethics committee of Ludwig-Maximilians University, Munich, Germany, as well as by the ethics committees of the participating medical centers. The following criteria were used to select the patients: a history of excessive axillary perspiration of more than 1 year, sweat production greater than 50 mg/min measured on at least 2 occasions by a standardized gravimetric procedure, and failure of 4 weeks of topical therapy with 10% or 20% aluminum chloride solutions applied daily. The exclusion criteria included the presence of neuromuscular disease, organic causes of hyperhidrosis such as hyperthyroidism, concomitant therapy for hyperhidrosis, intake of drugs affecting muscle tone or the autonomic nervous system, pregnancy, or presence of malignancy. After enrollment and written informed consent, the patients were assessed by gravimetry and asked to rate their own sweating before and after therapy using a visual analog scale consisting of a straight line of 100-mm lengths. The left end represented absolutely no sweating, while the right end represented maximal sweating. Patients were asked to mark a point anywhere on the scale according to their rating. Then, the visual score was measured in millimeters.

Gravimetric measurements were performed as described previously on at least 2 occasions before treatment and at every subsequent patient visit. Measurements were taken after the patient had rested for 15 minutes at room temperature (23°C±2°C). Before treatment, the actively sweating area was delineated by using the Minor iodine-starch test. The area was outlined with a waterproof skin marker. Ten prospective injection points within that area were marked in an even distribution. The units of botulinum toxin A herein specifically refer to Dysport and are not identical to units of other preparations of botulinum toxin A. Patients were treated with 200 U in one axilla and 100 U in the other according to a computerized randomization list in a double-blinded fashion. One vial of Dysport was dissolved in 5 mL of sodium chloride, yielding a final concentration of 100 U/mL. The 200-U side received 10 injections with 0.2 mL per point, while the 100-U side received 10 injections with 0.1 mL per point. Measurements of sweat production were obtained before and 2, 4, 12, 24, 36, and 48 weeks after treatment. Consequently, the patients were given a second treatment that was identical to the first one: the axilla that had received 200 U initially was treated again with 200 U, and the other axilla was treated again with 100 U.

Statistical analysis was performed using SAS software (version 6.12; SAS Institute Inc, Cary, NC). Absolute values of sweat production were the main outcome criteria. The paired t-test was used to compare sweat production in one axilla with production in the other. Relative sweat reduction was computed as the percentage of difference between baseline and post-treatment sweat rates. The Wilcoxon rank sum test was used to compare relative sweat reduction after 200 U and 100 U injections of botulinum toxin A.

Forty-three patients were included in the study (intention to treat), 37 of whom completed the 96 weeks of follow-up (per protocol). No patient discontinued the study for reasons related to the study medication or because of adverse effects. Baseline characteristics of the per-protocol population were as follows: 19 men and 18 women; age range, 19 to 64 years (mean age, 35 years); and mean body mass index, 24.3 (range, 18.2-32.2).

The baseline values of the hyperhidrotic area as delineated by the iodine-starch test as well as the values of sweat production as measured by gravimetry were comparable for both sides (Table 1). On injection of either 100 U or 200 U of botulinum toxin A, sweat production was significantly reduced, as confirmed 2 weeks after injection (Figure 1). There was no difference between 100 U or 200 U. At week 48, sweat production was back to baseline levels, irrespective of the amount of the dose (Figure 1). At this point, patients were given a second botulinum toxin A treatment in the same way as the first one: the axilla that had received 100 U initially was rein-

<table>
<thead>
<tr>
<th>Variable</th>
<th>100 U of BTA</th>
<th>200 U of BTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperhidrotic area, cm²</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>46.1 ± 29.4</td>
<td>46.3 ± 28.7</td>
</tr>
<tr>
<td>Minimum</td>
<td>14.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Median</td>
<td>31.4</td>
<td>37.7</td>
</tr>
<tr>
<td>Maximum</td>
<td>103.6</td>
<td>106.8</td>
</tr>
<tr>
<td>Sweat production, mg/min</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>168 ± 124</td>
<td>180 ± 116</td>
</tr>
<tr>
<td>Minimum</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Median</td>
<td>150</td>
<td>157</td>
</tr>
<tr>
<td>Maximum</td>
<td>560</td>
<td>518</td>
</tr>
</tbody>
</table>
jected with 100 U, and the axilla that had received 200 U was reinjected with 200 U. Sweat production again decreased significantly and gradually increased during the following 48 weeks (Figure 2), which added up to a total follow-up of 96 weeks. At each point (2, 12, 24, 36, and 48 weeks) after the second injection, there was no difference in sweat production when the 2 doses were compared (Table 2). Likewise, at each point, there was no difference in the patients’ rating of therapeutic success as measured by a visual analog scale (Figure 3).

To compare the efficacy and time course of the first and second botulinum toxin A treatments, the sweat production before treatment was defined as 100%, and subsequent reduction was calculated as the percentage of decrease. There was a significant difference between the first and second treatments for both doses: On the 200-U side, sweat production after 48 weeks had returned to 92% of baseline after the first treatment compared with only 66% after the respective follow-up of the second treatment (Table 3).

There was no serious adverse event during 96 weeks of follow-up. No patient withdrew from the study for treatment-related reasons. Minor adverse effects included stinging during injection, skin irritation, and mild fatigue after injection. All symptoms resolved without additional treatment in 1 to 4 days.

We conducted a randomized, multicenter clinical trial of a side-by-side comparison with 200 U and 100 U of botulinum toxin A injections in patients with axillary hyperhidrosis. Over a 96-week follow-up period in which patients were re-treated using the same side-specific doses, we found no difference in the results between the 2 doses at any given point. The results were established using gravimetric measurement of sweat production, which has become a standard objective parameter in clinical trials of hyperhidrosis.4,6,15,20,21 Also, patients’ rating of their sweating patterns was monitored according to a visual analog scale. Subjectively, the patients felt that their sweating after 36 weeks or more had come closer to baseline sweating compared with what could be measured objectively. An explanation for this finding may be that during the first months after treatment, patients hardly sweat at all. Thus, when sweating gradually returns, it is experienced as “close to as it has been before treatment,” even though it is objectively below baseline. This effect should be taken into consideration when treatment intervals are being determined. Nevertheless, both assessments, ie, gravimetry and patients’ ratings, showed al-

**Table 2. Comparison of Sweat Production After 200-U and 100-U Treatments With Botulinum Toxin A**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Mean Difference of Gravimetric Signed Rank Test Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200-U Side Minus</td>
</tr>
<tr>
<td>Week 0</td>
<td>−4.3</td>
</tr>
<tr>
<td>Week 2</td>
<td>−1.3</td>
</tr>
<tr>
<td>Week 12</td>
<td>1.7</td>
</tr>
<tr>
<td>Week 24</td>
<td>1.7</td>
</tr>
<tr>
<td>Week 36</td>
<td>0.3</td>
</tr>
<tr>
<td>Week 48</td>
<td>3.7</td>
</tr>
</tbody>
</table>

*The Wilcoxon signed rank test was used to compare side-matched differences in sweat production measured by gravimetry of axillae that were treated with 200 U or 100 U.
Treatment With 100 U, %

<table>
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<th>Time Point</th>
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<th>Second</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
<td>NA</td>
</tr>
<tr>
<td>Week 2</td>
<td>16 ± 13</td>
<td>10 ± 11</td>
<td>.36</td>
</tr>
<tr>
<td>Week 12</td>
<td>18 ± 16</td>
<td>21 ± 24</td>
<td>.83</td>
</tr>
<tr>
<td>Week 24</td>
<td>38 ± 28</td>
<td>33 ± 28</td>
<td>.76</td>
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<tr>
<td>Week 36</td>
<td>58 ± 32</td>
<td>39 ± 30</td>
<td>.33*</td>
</tr>
<tr>
<td>Week 48</td>
<td>92 ± 43</td>
<td>66 ± 33</td>
<td>.001*</td>
</tr>
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Abbreviation: NA, not applicable.

*Sweat production is expressed in percentage of pretreatment levels. The Wilcoxon signed rank test was applied to evaluate differences between corresponding points after the first and second treatments. All values other than P values are given as mean ± SD.

Table 3. Comparison of Percentage of Sweat Production After First and Second Treatments With Botulinum Toxin A

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<tr>
<td>Week 36</td>
<td>65 ± 75</td>
<td>36 ± 23</td>
</tr>
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<td>Week 48</td>
<td>98 ± 75</td>
<td>63 ± 32</td>
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Week 0 100 ± 0 100 ± 0 100 ± 0 100 ± 0 100 ± 0 NA

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tistical analysis: Heckmann and Gesellschaft für Therapieforschung, Munich, Germany. Administrative, technical, and material support: All authors.

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REFERENCES


Dermatology online with interactive technology is being offered as a free interactive e-learning platform for undergraduate and postgraduate students in dermatology and is available through www.swisdom.org. The editor of this platform is Professor G. Burg, with coeditors Professors T. Ruflf, R. Panizzon, L. Braathen, T. Hunziker, P. Elsner, S. Lautenschlager, and Drs J. Gorog, R. Kropfl, C. Cipolat, U. Bader, and C. Gerber. Coordinators are C. Mnich and V. Djamei. The interactive program is offered in English, French, and German with translations provided by Dr W. Burgdorf. Programming is provided by Arpage AG, Kusnacht/CH. For a free access account, please contact doi@usz.ch.