Botulinum Toxin A for the Treatment of Dyshidrotic Hand Eczema

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Abstract

Background: Dyshidrotic hand eczema is a relatively common vesicobullous disorder of the palms and soles. It is also known as pompholyx, dyshidrotic hand dermatitis, and palmoplantar eczema. It is characterized by pruritic lesions that can erupt in a chronic or relapsing pattern with episodes lasting months to years. The condition can be difficult to treat because of the thickness of the affected skin and the numerous sweat glands. Current treatments are not always effective and pose their own risks. Studies have shown associations between hyperhidrosis and dyshidrotic hand eczema. Botulinum toxin A (BTXA) has been used to treat hyperhidrosis with success. This leads to the possibility that BTXA may be an effective treatment option for refractory cases of dyshidrotic hand eczema.

Methods: An exhaustive search of available medical literature was conducted using Medline-OVID, EBMR Multifile, CINAHL, and Web of Science. The keywords dyshidrotic eczema, eczema, pompholyx, and botulinum toxins were used in the search. The relevant articles were evaluated for quality using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria.

Results: Two prospective control studies met inclusion criteria and were included in this systematic review. The first study investigated whether BTXA injections used with topical corticosteroids could treat dyshidrotic hand eczema better than topical therapy alone. Eight adult patients were enrolled with dyshidrotic hand eczema. Itching and vesiculation were inhibited earlier when using both BTXA and corticosteroids compared to corticosteroids alone. The second study evaluated the effects of BTXA injections as a treatment for dyshidrotic hand eczema with the other hand as an untreated control. Ten patients with bilateral hand eczema enrolled in the study. There were significant reductions in patient important outcomes and disease processes in the BTXA treatment hand compared to the control.

Conclusion: BTXA can be a reasonable treatment option for patients with refractory dyshidrotic hand eczema. This treatment may be even more valuable in patients with hyperhidrosis.

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Botulinum Toxin A for the Treatment of Dyshidrotic Hand Eczema

Rebecca J Schultz

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR For the Masters of Science Degree, August 9, 2014

Faculty Advisor: James Ferguson, PA-C Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Rebecca Schultz is a native of Washington where she majored in Kinesiology at Washington State University in 2010. She spent the next few years working as a CNA in Washington. She then moved to Wyoming with her husband and worked in the operating room. After completing PA school she plans to join her Husband in Alaska on the Kenai Peninsula. She enjoys hiking, fishing, and exploring both Alaska and Washington with her husband and dog. Her professional interests are family medicine, women’s health, and dermatology.
Abstract

Background: Dyshidrotic hand eczema is a relatively common vesicobullous disorder of the palms and soles. It is also known as pompholyx, dyshidrotic hand dermatitis, and palmoplantar eczema. It is characterized by pruritic lesions that can erupt in a chronic or relapsing pattern with episodes lasting months to years. The condition can be difficult to treat because of the thickness of the affected skin and the numerous sweat glands. Current treatments are not always effective and pose their own risks. Studies have shown associations between hyperhidrosis and dyshidrotic hand eczema. Botulinum toxin A (BTXA) has been used to treat hyperhidrosis with success. This leads to the possibility that BTXA may be an effective treatment option for refractory cases of dyshidrotic hand eczema.

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Keywords: Botulinum toxin A, dyshidrotic hand eczema, pompholyx
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List of Abbreviations

BTXA: Botulinum toxin A
GRADE: Grading of Recommendations, Assessment, Development and Evaluations
DASI: Dyshidrotic Eczema Area and Severity Index
VAS: visual linear analogue scale
Botulinum Toxin A for the Treatment of Dyshidrotic Hand Eczema

BACKGROUND

Dyshidrotic hand eczema is a vesicobullous disorder of the palms and soles.\textsuperscript{1} It is also known as pompholyx, dyshidrotic hand dermatitis, and palmoplantar eczema. It is characterized by pruritic lesions that can erupt in a chronic or relapsing pattern with episodes lasting months to years.\textsuperscript{2-4} The condition can be difficult to treat because of the thickness of the affected skin and the numerous sweat glands.\textsuperscript{1}

The current standard of care is topical corticosteroids. These often have to be used long term, which poses concerns. Other treatments that have been effective are calcineurin inhibitors, topical photochemotherapy, systemic photochemotherapy, or systemic corticosteroids. For refractory cases immunosuppressants have been used. All of these therapies pose risks of their own.\textsuperscript{1}

Dyshidrotic eczema can be difficult to treat, especially when triggers are difficult to avoid. The vesiculations are cosmetically concerning. More importantly they affect daily and occupational activities. The itching and burning is aggravating. It is not uncommon for excoriations to lead to secondary infections with staphylococci.\textsuperscript{1} It would be beneficial for a treatment to be longer lasting with fewer side effects.

The exact etiology of the disease has not been determined, however, there are a number of provoking factors. Sensitivity to nickel has been explored and appears to be an aggravating factor.\textsuperscript{5,6} Other factors include constant wetting of the hands, occlusion and sweating.\textsuperscript{2-4} Hyperhidrosis has been shown to be an aggravating factor in almost 40\% of cases and the disease is more common in the summer months.\textsuperscript{5} Sweating is regulated by
sudoriferic nerve endings. Acetylcholine is the major transmitter that stimulates eccrine gland activity. Botulinum toxin A (BTXA) is a selective and potent inhibitor of sudoriferic nerve endings. BTXA is able to inhibit acetylcholine release. Due to this mechanism BTXA has been used in past years to treat hyperhidrosis with success. Botulinum toxin A has the potential for use as a treatment for refractory cases of dyshidrotic hand eczema.

METHODS

An exhaustive search of available medical literature was conducted using Medline-OVID, EBMR Multifile, CINAHL, and Web of Science. The keywords dyshidrotic eczema, eczema, pompholyx, and botulinum toxins were used in the search. Articles that studied the treatment of dyshidrotic hand eczema using botulinum toxin A (BTXA) injections and were included for review. The reference list of each relevant article was reviewed for additional pertinent studies. The studies also only included English language studies and those with human subjects. These relevant articles were evaluated for quality using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria.

RESULTS

After combining the terms “eczema”, “dyshidrotic”, or “pompholyx” with “botulinum toxins” nine articles were retrieved. After reviewing for primary data and human studies, two articles met the inclusion criteria. Both articles were controlled prospective studies. See Table 1.

Wollina et al
This prospective controlled study\textsuperscript{12} investigated whether BTXA injections used with topical corticosteroids could treat dyshidrotic hand eczema. Eight adult patients were enrolled with atopic type dyshidrotic hand eczema. The study included five males and three females ages 29-32 years old. In all patients both hands were affected.\textsuperscript{12}

The eczema was evaluated based on a semi-objective grading system the Dyshidrotic Eczema Area and Severity Index (DASI).\textsuperscript{14} The DASI is based on number of vesicles, erythema, scaling, and itching, as well as the extent of the affected area. The maximum score is 60 points. This evaluation was done before treatment and after 1 week, 4 weeks, and 8 weeks.\textsuperscript{12}

Patients were also administered topical steroids that were selected based on the patient’s clinical presentation of the hand eczema. Each patient remained on the same topical steroid for the duration of the study and applied equally to both hands. The hand with the more severe DASI score was treated with BTXA injections in addition the topical preparation of steroid. “One hundred units of BTXA (Botox, Pharm Allergan, Germany) diluted with 2 mL physiological sodium chloride solution were injected intracutaneously in aliquots of 0.1 mL using a 30-guage needle along the fingers and in the palms.”\textsuperscript{12}

At 8 weeks, six patients completed the study. In the control hands, which only topical corticosteroids were applied, inconsistent and limited improvement was seen in five of six hands. One patient’s DASI score increased. Only two patients saw improvement where the DASI score was less than 10 points.\textsuperscript{12} See Table 2.

However, all six of the hands treated with topical steroids in addition to BTXA showed significant improvement. At 8 weeks, none of the six patients had a DASI score
above 10 points. The BTXA group also showed faster relief from itching than steroids alone.\textsuperscript{12} See Figure 1.

\textbf{Swartling et al}

This prospective controlled study\textsuperscript{13} evaluated the effects of BTXA injections as a treatment for dyshidrotic hand eczema. Ten patients, five women and five men, ages 22-61 years with bilateral hand eczema enrolled in the study. At the beginning of the trial seven patients were using topical steroids and one had used systemic steroids. All ten had history of vesicular hand dermatitis, however, two of the ten may have also had hand psoriasis. It was noted that six patients had experienced hyperhidrosis.\textsuperscript{13}

Patients were assessed using a semi quantitative evaluation of several variables. Each hand was evaluated for disease activity score based on the occurrence of erythema, scaling, infiltration, excoriation, crusting, and vesicles. Each trait was graded on a scale of 0-3 (0=none, 1=mild, 2=moderate, 3=severe), giving each hand a maximum score of 18. The extent of the dermatitis was also evaluated based on the total area affected. The same two investigators did these assessments before and after treatment. They evaluated the first patients together. Patients also estimated the effect of the BTXA injections on a 5-point scale (none, slight, moderate, good, or very good). They also used a visual linear analogue scale (VAS) to indicate the extent of their itching before and after the injections.\textsuperscript{13}

Prior to injection with BTXA, regional anesthesia of the ulnar and median nerves was administered. Either the right or left hand was injected with 20 microliters of BTXA, provided by Allergan Pharmaceuticals, every 15 mm on the volar aspects of the palms.
and fingers. See Figure 2. The average total injected BTXA was 162 units. The opposite hand was left untreated to act as a control for follow-up.\textsuperscript{13}

Two patients were lost to follow-up, one due to personal reasons and one due to failure of protocol. One patient was still evaluated with VAS before and after injections.\textsuperscript{13}

Patients were evaluated at follow up visit between 28-59 days after injection (average 39 days). At completion 7 of 10 patients self reported good or very good treatment effect. One patient reported slight and two had none. The VAS score for itching decreased by 39\% on the hand injected with BTXA and increased by 52\% on the untreated control hand. The disease activity score decreased by 54\% on the treated side and by 29\% on the untreated. The occurrence of vesicles decreased by 74\% on the treated side and 27\% on the untreated side. Erythema was decreased by 53\% on the treated side and 30\% on untreated side. The extent of disease was decreased by 58\% on the treated side versus 27\% on the untreated side. There was minimal or no change seen in scaling, crusting, and excoriations.\textsuperscript{13} See Table 3.

**DISCUSSION**

The data presented above indicates that botulinum toxin A may be an alternative treatment option for patients with dyshidrotic hand eczema. Patients with refractory cases of this disorder may benefit most from this treatment. Furthermore, using BTXA may confer longer lasting benefit than other topical therapies such as corticosteroids. The Swartling et al study\textsuperscript{13} did report the side effect of minimal transient muscle weakness in the hand.\textsuperscript{13} No other side effects were reported in either study. The use of regional anesthesia would greatly reduce pain and discomfort to the patient making this treatment option more tolerable.
It was observed in the Swartling et al study\textsuperscript{13} that patients with noted hyperhidrosis benefitted most from the treatment with six out of the seven patients that reported good or very good results having hyperhidrosis. While the etiology of dyshidrotic hand eczema is not completely clear, there does appear to be a link between sweating and the disease process. This could be due to sweat aggravating the skin and inducing itch in the atopic patient.\textsuperscript{13} The Wollina et al study\textsuperscript{12} also demonstrated that by interrupting sweating the hand eczema was able to heal. BTXA has been shown to decrease sweating and has been used for focal hyperhidrosis with success.\textsuperscript{9,10,15} In recent studies\textsuperscript{16,17} it has been shown that substance P release is also inhibited by BTXA, which may explain the antipruritic activity.

Although both studies\textsuperscript{12,13} demonstrated promising results, there were limitations to both studies. In Wollina et al\textsuperscript{12} there was no allocation concealment. The hand with a more severe DASI score was used at the treatment hand, which may increase the chance of bias. There was also no blinding or randomization. Allocation concealment would have been difficult to accomplish, as the effects of BTXA are noticeable, such as transient weakness and anhidrosis. Nevertheless, no attempt was made to blind either patient or administer which may lead to performance bias. Patients also started the study with a range of disease severity. They were subsequently treated with different topical corticosteroid preparations. This could lead to performance bias, although unlikely as one hand acted as control. The use of the DASI provided a relatively objective scoring system and decreases detection bias. The study went to completion of 8 weeks. The small sample size of six patients completing the study seriously limits the precision. There is also the possibility of publication bias as the study was funded by a grant from Allergan.
Pharmaceuticals, which produces Botox and provided its product for this study. This study was assessed using GRADE and due to these limitations its quality was determined to be very low.\textsuperscript{11,12}

The Swartling et al study\textsuperscript{13} also demonstrated limitations. There was no allocation concealment, randomization, or blinding but with the use of one hand as treatment control it is unlikely that the study design had significant implications on the treatment effect. All patients were injected with same amount of BTXA, decreasing likelihood of performance bias. However, at the start of the trial 7 of the 10 patients had been on topical steroids and one of those had also used systemic steroids. This could impact results. Outcomes were measured with a semi-objective disease activity and extent of dermatitis grading system. The use of use of a VAS for itching and self-estimation of treatment is relatively objective and introduces some level of detection bias. The same two investigators assessed patients using their scoring system, but did so separately after the first few patients also introducing some level of bias. The article does not disclose how the hand was chosen to receive treatment and does not take into account the difference in disease severity. There are slight prognostic differences between hands, most notably in the VAS for itching. See Table 3. The small sample size of 10 patients is a serious limitation to the precision of the study. It is unlikely that there is publication bias as funding was through county councils in Sweden. Botox product was supplied for the study from Allergan Pharmaceuticals. Overall, the quality of evidence was determined to be very low using GRADE.\textsuperscript{11,13}

Despite each study’s limitations the use of patient important outcomes and having a control ameliorates some concerns over the low quality of evidence. Having a double-
blind study with placebo versus BTXA would be ideal. Further studies may benefit from larger population size.

**CONCLUSION**

Botulinum toxin A has demonstrated to have strong potential to be a treatment for refractory cases of dyshidrotic hand eczema. The effectiveness and longevity of the treatment is promising. With use of regional anesthesia the process would be less problematic. Cost may be a barrier to treatment and make its use as the standard of care unlikely when corticosteroids are relatively low priced. Research to further knowledge of BTXA for this type of eczema is needed before it will likely become common practice for refractory cases. However, in refractory cases it should be considered as a valuable treatment option.
References


11. Available at: http://gradeworkinggroup.org/.


Table 1. GRADE evidence profile: Botulinum toxin A for treatment of dyshydrotic hand eczema

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Downgrade Criteria</th>
<th>Quality</th>
<th>Importance</th>
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<tbody>
<tr>
<td>Design</td>
<td>Limitations</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td>Wollina et al study</td>
<td>Prospective Controlled</td>
<td>Serious limitations</td>
<td>Serious indirectness</td>
</tr>
<tr>
<td>Reasoning</td>
<td>No blinding, no allocation concealment, no randomization</td>
<td>Use of different adjuvant therapies</td>
<td>Small sample size, No CI given</td>
</tr>
<tr>
<td>Swartling et al study</td>
<td>Prospective controlled</td>
<td>Serious limitations</td>
<td>Serious indirectness</td>
</tr>
<tr>
<td>Reasoning</td>
<td>No blinding, no allocation concealment, no randomization</td>
<td>Small sample size, no CI given</td>
<td>No disclosure how treatment hand was chosen</td>
</tr>
</tbody>
</table>

Table 2. Improvement of Dyshidrotic Eczema Area and Severity Index score in dyshidrotic hand eczema: pretreatment vs. 8 weeks of follow-up adapted from Wollina et al study.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Topical corticosteroids</th>
<th>Topical corticosteroid plus botulinum toxin A</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>18</td>
</tr>
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<td>3</td>
<td>9</td>
<td>8</td>
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<td>4</td>
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<td>5</td>
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<td>8</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>Mean</td>
<td>28</td>
<td>17</td>
</tr>
</tbody>
</table>
Table 3. Summary of findings adapted from Swartling et al study.\textsuperscript{13}

| Patient | Pruritus Score (VAS) | | Vesicle Occurrence | | Total Activity Score | | Effect |
|---------|----------------------|------------------|-------------------|----------------------|------------------|---------|
|         | Treated | Untreated | Treated | Untreated | Treated | Untreated | Treated | Untreated | Treated | Untreated | Treated | Untreated |         |
|         | Before  | After    | Before  | After    | Before  | After    | Before  | After    | Before  | After    | Before  | After    |         |
| 1       | 7.3     | 1.2      | 7.3     | 7        | 3       | 0        | 3       | 3        | 11      | 2        | 11      | 10       | Good    |
| 2       | 1.5     | 0        | 1.5     | 2.3      | 2       | 1        | 2       | 1        | 4       | 2        | 4       | 4        | Good    |
| 3       | 5       | 2.5      | 5       | 5        | 2       | 0        | 2       | 1        | 9       | 2        | 9       | 4        | Good    |
| 4       | 2       | 0.2      | 2       | 8        | -       | -        | -       | -        | -       | -        | -       | -        | Very good |
| 5       | 2.1     | 9.1      | 2.4     | 5.3      | 0       | 0        | 0       | 0        | 2       | 5        | 2       | 4        | None    |
| 6       | 3.2     | 0        | 3.2     | 0.5      | 1       | 0        | 1       | 1        | 6       | 3        | 6       | 6        | Good    |
| 7       | 3.9     | 3.6      | 2.5     | 2        | 3       | 2        | 3       | 1        | 11      | 7        | 11      | 5        | None    |
| 8       | 0.8     | 2.2      | 3       | 4.8      | 1       | 0        | 1       | 0        | 6       | 3        | 6       | 3        | Slight  |
| 9       | 5       | 0        | 1       | 7.6      | 3       | 1        | 3       | 3        | 9       | 4        | 9       | 7        | Good    |
| 10      | 0.4     | 0.2      | 0.5     | 0.7      | 0       | 0        | 0       | 1        | 7       | 1        | 7       | 3        | Very good |
| Median  | 2.6     | 0.7      | 2.4     | 4.9      | 2       | 0        | 2       | 1        | 7       | 3        | 7       | 4        | Good    |
Figure 1. Improvement of Dyshidrotic Eczema Area and Severity Index score with topical corticosteroids alone (a) and adjuvant botulinum toxin A (b) adapted from Wollina et al study.¹²

a.

b.
Figure 2. Adapted schematic view of injection sites of BTXA from Swartling et al study.