
Duration of efficacy increases with the repetition of botulinum toxin A injections in primary palmar hyperhidrosis: A study of 28 patients

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Background: Intradermal injections of botulinum toxin are effective but transitory in primary palmar hyperhidrosis. These injections are repeated when the symptoms recur. We do not know how the duration of efficacy changes when injections are repeated.

Objective: In this retrospective study, we aimed to investigate the change in the duration of efficacy of botulinum toxin A (Dysport, Ipsen, Boulogne-Billancourt, France) with the repetition of injections in patients with primary palmar hyperhidrosis.

Methods: From May 2001 to April 2012, 28 patients were treated with a dose of 250 U of botulinum toxin A per palm. We compared the duration of efficacy of the first and last toxin injections.

Results: The median duration of efficacy was 7 months for the first injection and 9.5 months for the last, the difference being statistically significant ($P = .0002$).

Limitations: Study limitations include a relatively small number of patients treated at a single center and evaluated retrospectively.

Conclusion: To our knowledge, this study is the first to report a significant increase in the duration of efficacy of botulinum toxin A injections with the repetition of injections in patients with primary palmar hyperhidrosis. The reasons for this effect may be linked to the mechanism of action of botulinum toxin, and may improve our understanding of its pharmacologic effects. (*J Am Acad Dermatol* 2014;70:1083-7.)

Key words: axillary; botulinum toxin; duration of efficacy; hyperhidrosis; increase; repetition of injections.

Hyperhidrosis is excessive production of sweat affecting 1% to 3% of the population, with a sex ratio of 1, and is most prevalent among those aged 25 to 64 years.¹⁻³ It can have major psychosocial repercussions for patients.⁴⁻⁶ It is mostly idiopathic (primary) but may be associated with an underlying disease. It is localized in 90% of cases,⁷ but it may also be generalized. The regions of the body most affected are the underarms, palms of hands, soles of feet, forehead, and inguinal folds. Sweat is secreted and excreted by the eccrine sweat

glands, which are innervated by cholinergic fibers, paradoxically, via the sympathetic system. The first-line local treatments are antiperspirants based on aluminium salts, which often prove ineffective, and iontophoresis. Intradermal injections of botulinum toxin are used as a second-line treatment and have been shown to be effective⁸ by blocking the presynaptic release of acetylcholine. These injections are repeated when the symptoms recur. Treatment has been reported to be effective for about 2 to 22 months, but nothing is known about the change in

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the duration of efficacy with repeated injections.⁹⁻¹⁵ Endoscopic thoracic sympathectomy is a possible invasive treatment, which is offered in severe cases, after the failure of other medical treatments. It frequently causes compensatory hyperhidrosis. It is also an expensive treatment. The aim of this retrospective study was to evaluate the changes in the duration of efficacy of botulinum toxin injections for palmar hyperhidrosis with the repetition of injections.

METHODS

We included all eligible patients followed up for primary palmar hyperhidrosis and seen between May 2001 and April 2012 in dermatology consultations at Le Mans Hospital in France for treatment with botulinum toxin.

All the patients had experienced failure for first-line treatment with antiperspirants based on aluminum salts with concentration at 20% and/or iontophoresis, with major psychosocial repercussions.

All these patients had palmar hyperhidrosis detected by Minor test.¹⁶ In this test, 2 g of iodine and 4 g of potassium iodide in alcohol to 100 mL is painted over the skin area. After it has dried, a fine starch powder is applied. Sweat causes the color to turn dark blue. The result is measured over 5 minutes at room temperature and at rest. In all cases the iodine-starch test made it very easy to identify the location of excessive sweating in the palmar skin (Fig 1).

All had a Hyperhidrosis Disease Severity Scale (HDSS) score of more than 2/4, indicating severe hyperhidrosis and that sweating interfered with activities of daily living. It is a disease-specific scale for hyperhidrosis that provides a qualitative measure of the severity of the patient's condition based on how it affects daily activities. A score of 1 corresponds to: "my palm sweating is never noticeable and never interferes with my daily activities"; a score of 2 corresponds to: "my palm sweating is tolerable but sometimes interferes with my daily activities"; a score of 3 corresponds to: "my palm sweating is barely tolerable and frequently interferes with my daily activities"; and a score of 4 corresponds to: "my palm sweating is intolerable and always interferes with my daily activities." The validity and reliability of the HDSS were proved, and the use of this scale is recommended by the Canadian Hyperhidrosis Advisory Committee.⁸

The exclusion criteria were myasthenia and pregnancy. All patients underwent a pretreatment evaluation consisting of a clinical examination, objective excessive sweating, with criteria of primary hyperhidrosis (focal, visible, excessive sweating of at least 6 months' duration without apparent cause with at least 2 of the following characteristics: bilateral and

relatively symmetric, impairs daily activities, frequency of at least 1 episode per week, age of onset <25 years, positive family history, cessation of focal sweating during sleep).¹⁷ An evaluation, including a clinical examination, thyroid palpation, and determinations of glycemia and thyroid stimulating hormone, was carried out to exclude cases of secondary hyperhidrosis.

All patients were treated with a first injection of botu-

linum toxin A (Dysport) at a dose of 250 U per palm. The botulinum toxin (500 U) was diluted in 2.5 mL of saline and 1-mL syringes fitted with a 30G needle were used for the injections. In total, 25 intradermal injections of 0.05 mL of botulinum toxin A (10 U) were administered, separated by a distance of 1 to 2 cm, into each palm and the fleshy parts of the fingers. We offered the patients pain relief, based on the inhalation of an equimolar mixture of nitrogen and oxygen or hypnoanalgesia, during the injection sessions. Subsequent sessions were performed at the patient's request, when the symptoms recurred with moderate discomfort (HDSS score >2/4) with a positive Minor test result. The HDSS score and Minor test result were evaluated at each visit. During these successive sessions, the duration of efficacy of the previous injection was evaluated by asking the patients how long it took for the symptoms to recur.

We compared the median duration of efficacy of the first and last injections of botulinum toxin. We determined median rather than means, because the median is considered more reliable than the mean for analyses of time intervals, which are generally asymmetrically distributed. Indeed, the presence of an extreme value in 1 individual has a considerable effect on the mean value, but little or no effect on the median value.

We used nonparametric Wilcoxon matched pair tests to compare the durations of efficacy between the first and last injections, with a significance threshold of 5%. Statistical analyses were carried out with R software.¹⁸

CAPSULE SUMMARY

- Injections of botulinum toxin are effective but transitory in primary palmar hyperhidrosis.
- We report a significant increase in the duration of efficacy of botulinum toxin with the repetition of injections.
- This finding provides additional evidence about the long-term effectiveness. Patients can expect a decreased need for injection sessions over time.



Fig 1. Treatment of palmar hyperhidrosis with botulinum toxin A: Minor test performed 1 month after injection of Dysport in palm and pulp of the fingers of the right hand. Sweat causes the color to turn black. Note the decreased sweat on the right hand compared with the untreated left hand.

RESULTS

We included 28 patients, 17 female and 11 male, aged from 17 to 73 years, between May 2001 and April 2012. The median duration of efficacy was 7 months for the first injection and 9.5 months for the last injection (Fig 2). The difference between these 2 values was statistically significant ($P = .0002$; Wilcoxon matched pair tests). The patients underwent a mean of 4 injection sessions: 24 patients (86%) had 2 to 5 sessions, 2 patients had 6 sessions, 1 patient had 8 sessions, and 1 patient had 11 sessions. For 1 patient there were only 2 injection sessions, and thus the second injection session was also the last. The mean duration of follow-up was 3.92 years (range: 5 months to 9 years). Overall, 18 patients were followed up for less than 5 years, 4 of whom were followed up for less than 1 year. Five patients were followed up 5 years. Five patients were followed up for at least 6 years, including 2 followed up for 9 years. The minimum and maximum values for the duration of efficacy of the first injection were 2.5 months and 14 months, respectively. The minimum and maximum durations of efficacy for the last injection were 3 months and 30 months, respectively. None of the patients reported major adverse effects. In particular, there was no compensatory sweating, myalgia, itching, or headache. Two patients presented a decrease in the muscular force of their fingers, which lasted 3 weeks in 1 case and 4 in the other and none required treatment cessation or a decrease in the dose used.

DISCUSSION

Many studies have demonstrated the efficacy and safety of botulinum toxin use in the treatment of primary palmar hyperhidrosis,^{9,12-14,19-23} but our study is the first to our knowledge to suggest an increase in the duration of efficacy of botulinum

toxin for palmar hyperhidrosis with repetition of injections.

This treatment improves the patient's quality of life,²³ which is often affected because of major socioprofessional consequences of this condition. The major drawback of this treatment is pain during the injections.^{13,20,24} Various analgesic techniques have been proposed, including nerve blocks, dilution of the botulinum toxin in lidocaine, and hypnosis.²⁵ Complications are rare and not very severe. In particular, patients may experience transient muscle weakness in the hands,^{22,26,27} but it does not prohibit further treatment sessions. No case of compensatory sweating in untreated zones has been described in patients treated by botulinum toxin injections (Botox, Allergan, Inc, Irvine, CA) for palmar hyperhidrosis.²⁸ This adverse effect, which is frequent after thoracic sympathectomy (50%-80% of patients),²⁹⁻³² is rarely reported after injections of botulinum toxin A (5% of patients according to Naumann and Lowe³³).

The reported duration of efficacy differs between studies, from 2 to 22 months.^{9,12,22,24} One study suggested that there was a relationship between the dose of toxin injected and the duration of efficacy: high dose of botulinum toxin (200 U Botox per palm) was associated with a significantly more long-term remission than low-dose therapy, but the comparison was made with published data rather than with matched groups. These high doses did not seem to increase the frequency of acute or long-term side effects.⁹

The repetition of injections does not lead to a decrease in efficacy. This was confirmed by Schnider et al²⁶ in a study of 61 patients treated over a period of 3 years for axillary or palmar hyperhidrosis, at a dose of 230 mU botulinum toxin A (Dysport) per palm for palmar hyperhidrosis. An interval of at least 3 months was maintained between consecutive injection sessions, to prevent the production of neutralizing antibodies. The median time interval between the sets of injections was 25 weeks. Eight patients received more than 3 set of injections. Subjective evaluations after the first, second, and third sets of injections revealed no significant difference in subjective efficacy ($P = .68$) or in duration of efficacy ($P = .69$) between these injections. Schnider et al²⁶ may not have been able to demonstrate a significant difference in duration of efficacy because their follow-up period was much shorter than ours. In the study by Wollina and Karamfilov⁹ the follow-up did not exceed 23 months: the follow-up after second injection (within 3-8 months) was too short to be able to comment on the duration of effect.

It has been suggested that neutralizing antibodies may be produced after repeated injections of

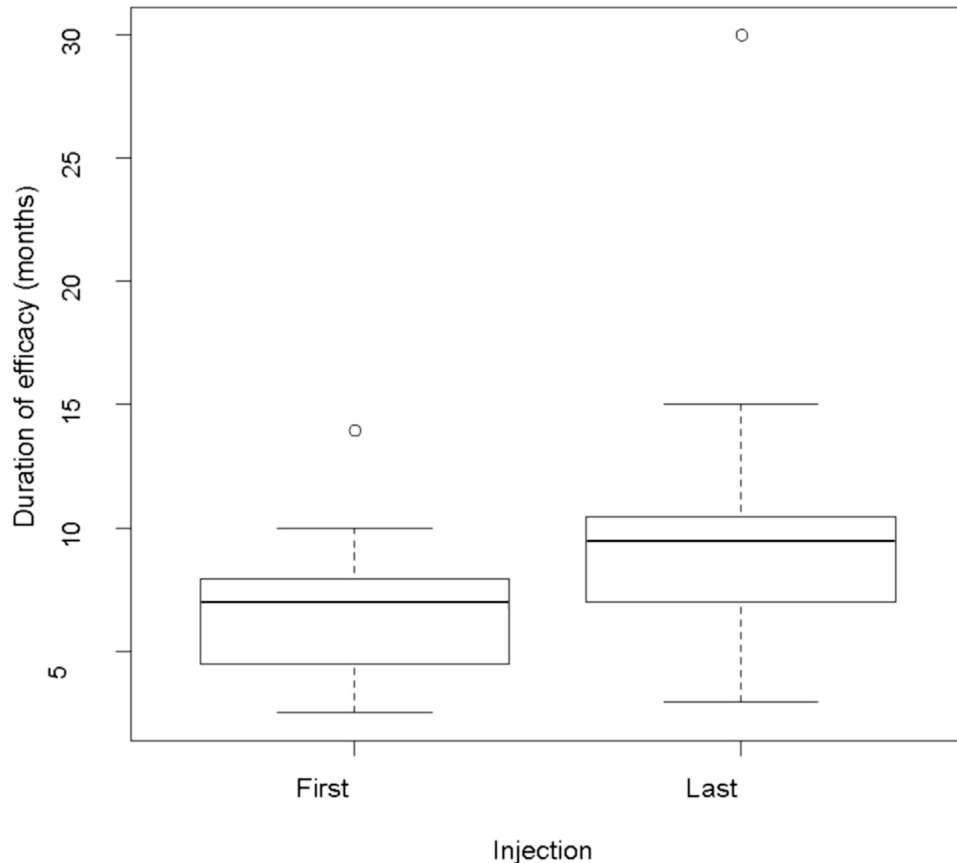


Fig 2. Box-and-whisker plots of the duration of efficacy of the first and last injections of botulinum toxin. Bold line = median duration; horizontal lines of the box = quartiles; upper and lower horizontal lines = maximum and minimum values, respectively; points = outliers.

botulinum toxin. Indeed, this toxin is bacterial in origin and it is therefore physiologically plausible that it could induce an immune response and the generation of antibodies. The factors potentially favoring antibody development are a high dose at each injection session, the total cumulative dose, a short interval between consecutive injection sessions, and the protein formulation of the toxin.³⁴ In a meta-analysis evaluating the frequency of neutralizing antibody conversion with botulinum toxin (Botox) across hyperhidrosis and neurologic indications, 11 of 2240 patients converted from antibody negative at baseline to positive at 1 or more posttreatment time points, but only 3 patients became clinically unresponsive to treatment. For primary axillary hyperhidrosis, only 4 of 871 patients (0.46%) presented seroconversion.³⁵ Antibodies were not detected in any of the patients treated for palmar hyperhidrosis. In our study, on a large number of patients with a long follow-up period, we did not check for the formation of antibodies, but the increase in the duration of efficacy with repeated injections is not consistent with a hypothetical

neutralizing activity because of antibodies. When the botulinum toxin blocks the synapse at the motor plate, it destroys one of the proteins required for the fusion of synaptic vesicles with the membrane. This leads to a degeneration of the motor axon terminal. This terminal gradually grows back, accounting for the transient nature of the effect of the botulinum toxin.³⁶ We hypothesize that the increase of duration of efficacy with the repetitions of injections occurs as a result of slowing regrowth of axon terminal of the motor neuron.

CONCLUSION

To our knowledge, our study is the first to suggest an increase in the duration of efficacy of botulinum toxin A for primary palmar hyperhidrosis with the repetition of injections, and in axillary hyperhidrosis.³⁷ This is supported by a statistically significant increase in the duration of efficacy with the repetition of injections from a retrospective review of 28 patients with primary palmar hyperhidrosis seen between May 2001 and April 2012 in dermatology consultations at Le Mans Hospital, France. To our

knowledge, it is the only study to have evaluated botulinum toxin in palmar hyperhidrosis over such a long period (11 years). The value of this treatment is supported by this study, which also confirms the absence of adverse effects in the long term.

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