

Diffusion and Short-Term Efficacy of Botulinum Toxin A After the Addition of Hyaluronidase and Its Possible Application for the Treatment of Axillary Hyperhidrosis

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BACKGROUND. Botulinum toxin adequately treats hyperkinetic facial lines and hyperhidrosis. Higher doses of botulinum toxin appear to enhance efficacy and longevity possibly through greater evenness of diffusion; however, recurrent treatments with higher doses are expensive.

OBJECTIVE. To admix botulinum toxin with hyaluronidase and to test whether there is maintenance of efficacy, a spread of effect, and possibly a decrease in required dose compared with botulinum toxin.

METHODS. Six patients participated in a double-blinded side-to-side comparison pilot study with photographic analysis for

frontalis overactivity and Minor's iodine and gravimetric testing for axillary hyperhidrosis.

RESULTS. Initial efficacy of botulinum with admixed hyaluronic acid appeared maintained with possibly increased diffusion when hyaluronic acid is added. No difference was evident on short-term review of patients treated with 50 U of botulinum in one axilla compared with the contralateral side injected with 25 U with admixed hyaluronidase.

CONCLUSION. There may be a role for hyaluronic acid in aiding diffusion and decreasing the required dose of botulinum toxin in hyperhidrosis axillaris.

THE BOTULINUM TOXIN AND SOME OF THE EQUIPMENT USED IN THIS STUDY WERE PROVIDED BY ALLERGAN.

BOTULINUM TOXIN has been found to be useful for many different medical and cosmetic conditions¹⁻¹⁴ and has also been shown to be effective in the treatment of some cases of hyperhidrosis; it is arguably best applied to axillary hyperhidrosis.

Hyperhidrosis may rarely be due to diseases such as hyperthyroidism or pheochromocytoma, and some occur as gustatory associated disease;^{15,16} however, most are idiopathic. Idiopathic hyperhidrosis affects 0.5% to 1% of the population, and patients often suffer enormous psychosocial stress in their working and private lives.^{17,18} This affliction is a physiologic one, not a psychiatric or endocrinologic disease, and reaches a peak in the 2nd and 3rd decades, with 60% of patients suffering predominantly palmoplantar disease and 30% to 40% affecting the axilla.¹⁹ For axillary hyperhidrosis, more than 50 mg of perspiration over 5 minutes is considered abnormal. Treatments have been both medical and surgical. Topical and systemic anticholinergics for axillary disease are criticized as being often ineffective²⁰ but often worth trying in milder cases. They are not totally benign with stinging often limiting topical antiperspirants. Oral anticholinergics such as Glycopyrronium bromide

may induce a number of unwanted side effects. Surgical treatments for axillary hyperhidrosis include endoscopic transthoracic sympathectomy, axillary vault dissection, and liposuction with or without curettage.²¹ These procedures all carry risks and varying levels of satisfaction with the procedures performed.²²⁻²⁵

Botulinum toxin injected into the skin aims to deliver an even dose of the agent across a broad area of eccrine sweat glands in axillae, palms and soles, and elsewhere, as required such as gustatory or focal sweating diseases. It may be that recurrence occurs because the dose has peaks of concentration near the insertion and the concentration falls away progressively until it meets the concentration gradient of the neighboring injection point. If the concentration at this junction is not similar, this junction point will receive a lesser dose and be likely the point of recurrence of the hyperhidrosis. Increasing the dose is one way, albeit expensive, of ensuring an adequate dose to the entire region; however, another way is being investigated here. If the spread of botulinum toxin can be maximized and thus the concentration reasonably constant over a broad area, it may reasonably be theorized that the desired effect may be achievable with a smaller dose of botulinum, allowing more patients to avail themselves financially of this treatment.

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Hyaluronidase is an enzyme and is widely distributed in nature.²⁶ It is usually derived from testicular tissue extracts.²⁷ In the case of this study, the material is produced from sheep testes (Hyalase; Aventis Pharma, Lane Cove, NSW, Australia).

Hyaluronidase seems a very safe agent and is usually used in two clinical scenarios. The enzyme breaks down hyaluronic acid in connective tissue, increasing tissue permeability, and is commonly used in ophthalmologic eye blocks with local anesthesia;²⁸⁻²⁹ it may not only be useful in augmenting the local anesthesia but is also possibly protective of skeletal muscular toxicity associated with local anesthesia alone.^{30,31} Hyaluronidase may also have a protective role in decreasing skeletal muscle damage associated with electrotransfer of plasmid gene transfer into these skeletal muscles.³²

It is also commonly used for the treatment of extravasated materials whether that is sclerotherapy agents,^{33,34} antineoplastic agents, or other toxic compounds.³⁵⁻³⁷ In neonates, hyaluronidase is used in the management of intravenous extravasations of total parenteral nutrition, 10% dextrose injection, calcium salts, potassium salts, sodium bicarbonate, aminophylline, radiocontrast media, nafcillin, and hypertonic saline.³⁸

We use axillary hyperhidrosis as our study model, but similar models could be envisaged with any broad area of cholinergic receptor activity such as other areas of hyperhidrosis or large skeletal muscles.

This small study has several aims: (1) It attempts to confirm the efficacy botulinum toxin admixed with hyaluronidase. (2) If the mixture remains potent, then we aim to test whether hyaluronidase can increase the spread of botulinum toxin. (3) If spread is increased by hyaluronidase, then assessment is given as to whether this translates into a decreased dose of botulinum toxin being required to induce and maintain the same or similar result. (4) If spread is increased, then it may be that a more even diffusion is attained. If recurrence is due to breakthrough in the relatively less concentrated area between injection points, then a more even spread may induce a longer remission. This will be examined in a later study, as will longevity of results.

Methods

Patient Profile

Six patients have been treated in the pilot study. The first was injected with 5 U (0.15 mL) of botulinum toxin (3-mL dilution with preserved saline) into the left forehead and 5 U with 0.05 mL of superadded hyaluronidase (75 U) into the right side. This is to assess whether there is inactivation of the toxin by

hyaluronidase. Frontal muscular activity will be assessed by photography for wrinkle effacement over a 2-week period. This patient was injected with 15 U in total to four premarked regions of the infraorbital region using botulinum toxin (100 U per 5 mL of preserved saline) compared with botulinum toxin (100 U per 4.8 mL of preserved saline and 0.2 mL or 300 U of water-diluted hyaluronidase). This latter injection was performed 1 week after the solution had been prepared and kept in 1-mL tuberculin syringes.

The second patient was injected into their axillae with a single injection into each axilla performed in a double-blinded fashion with a Minor's iodine test performed at baseline and at 2 weeks. The dilution was 100 U of botulinum toxin in 5 mL of preserved saline for the botulinum toxin side and 4.8 mL of preserved saline and 0.2 mL of hyaluronidase (300 U) for the opposite side. Ten units (0.5 mL) were injected in a single injection in the axillary vault. Sweat production was measured at baseline in each axilla by gravimetric scale weighing of filter paper. After 2 weeks and after assessing the Minor's iodine test and total weighed sweat production, the code for this patient was broken, and this patient was treated in open fashion but was otherwise as indicated as per patient 3.

The third patient had 50 U of botulinum toxin (2.5 mL) at the same dilution as patient 2 injected at approximately 1-cm intervals into 25 injection sites. The other axilla was similarly injected with the solution of botulinum toxin containing hyaluronidase again in a double-blinded fashion.

The fourth patient was injected with 25 U of botulinum toxin (1.25 mL) at the same dilution as patient 2 injected at approximately 1-cm intervals into 25 injection sites. The other axilla was similarly injected with the solution of botulinum toxin containing hyaluronidase again in a double-blinded fashion. If the outcome was not deemed sufficient, the patient was to be treated again with reversal of the treatments with one axilla to receive 25 U of botulinum toxin with hyaluronic acid and the other to receive 50 U of botulinum. In this treatment, the blinding is continued by the dilution of the botulinum toxin with 100 U diluted by 9 mL of preserved saline and 1 mL of hyaluronic acid dissolved with sterile water. The botulinum was diluted 100 U in 5 mL of preserved saline alone; 2.5 mL of each solution was injected. This higher concentration of hyaluronic acid (10% rather than 4%) was used for the remainder of this limited pilot study.

Patients 5 and 6 were injected with 50 U of botulinum toxin (2.5 mL) of a mixture containing 100 U of botulinum toxin per 5 mL in one axilla, whereas the other axilla was injected with 25 U (2.5

mL) of a mixture containing 100 U of botulinum toxin diluted with 9 mL of preserved saline and 1 mL of hyaluronidase (1,500 U).

In all circumstances in which double masking was required, this was accomplished by blinding the patient and the assessor as to the treatment received. Patients 2 to 6 had the same unmarked syringes and the same volumes and injection methods when hyaluronic acid was used as compared with when it was not; therefore, the injector was considered also to be blinded or masked as to the material. The code was broken 2 weeks after the last patient had been injected to assess efficacy. Longevity is not being assessed in this early phase article but will be assessed as an open-phase extension and reported in a later article.

Material Preparation

Diluted botulinum toxin type A (Botox; Allergan, Irvine, CA) was prepared from a frozen vial of botulinum toxin containing 100 IU. To this was added 3, 5, or 10 mL of 0.9% benzoyl alcohol-preserved saline without shaking the vial. This led to a concentration of 3.3, 2, or 1 U per 0.1 mL of solution. This was then drawn up into 10 1-mL syringes containing 10 U in each syringe.

The following were included in the objective analysis: gravimetric sweat testing at baseline and at 2 weeks and each month thereafter (Figure 1); digital photography, using the Minor's Iodine test at same appointment; assessment of injection discomfort at time of injection and at the 2-week visit; and assessment of any minor or major adverse events.



Figure 1. Patient 1 showing progressive effects of a single injection of 5 U of botulinum toxin with hyaluronidase on the right side and 5 U of botulinum toxin along on the left side. Photographs are at preinjection, at Day 5, at Day 7, and at Day 14 showing a slightly wider circle of effect on the right side of the forehead.

Results

The first patient (Figure 1) showed effect of the botulinum toxin on both sides of the forehead where 5 U were injected into the midforehead. The right side that was injected with botulinum toxin with superadded hyaluronidase appearing to have a larger circle of effect at all postinjection reviews.

The first patient was also injected with 15 U with (right side) and without hyaluronidase (left side) in the periorbital zone with equivalent results at 2 weeks, although the result appeared somewhat delayed at onset on the side injected with superadded hyaluronidase.

Patient 2 (Table 1) who had 10 U of botulinum as a single injection to the right axilla was noted to have her 5-minute sweat test decrease from 163 to 10 mg (153-mg decrease). The left side injected with 10 U of botulinum and superadded hyaluronidase also showed a decline sweating from 160 to 12 mg per 5 minutes (148-mg decrease). The minor's iodine test appeared more positive than that indicated by the gravimetric sweat testing. These two first patients suggested that initial efficacy of the toxin at 2 weeks was not significantly lessened. Further injection of 25 U of the same agents into the same axillae made little further impact on the sweating test levels but decreased the sweating visible on minor's iodine test (Figure 2).

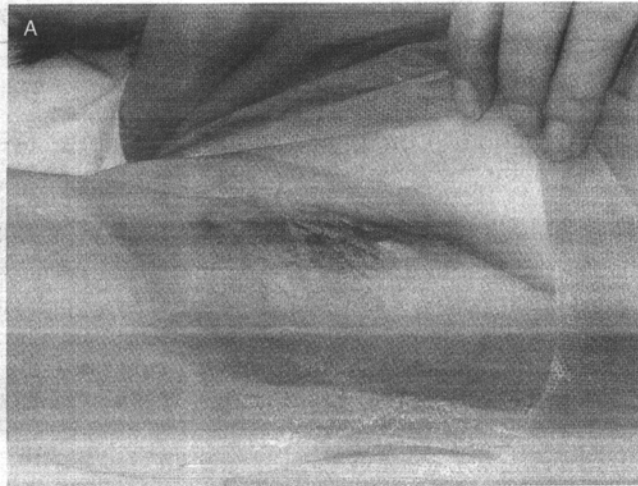
The third patient had a discrepancy between her rates of sweat production, with her right axilla showing a preinjection sweat rate of 143 mg on the right side and 28 mg on the left side in the 5-minute gravimetric test. She had 50 U of botulinum toxin, with hyaluronidase injected into the right axilla and 50 U of botulinum toxin injected into the left axilla. At the posttreatment review, a decrease to anhidrosis (less than 1 mg per 5 minutes) on the right side (Figure 2) and anhidrosis (less than 1 mg per 5 minutes) on the left side was noted (Table 1).

The fourth patient who had very significant hyperhidrosis was injected with 25 U of botulinum toxin without (right axilla) and with added hyaluronidase (left axilla). There was a substantial decline in sweating from 503 to 70 mg in the right axilla (433-mg decrease) and a similar decrease in the left axilla from 389 mg to a less hidrotic state of 22 mg (367-mg decrease).

Further injection was performed at 6 weeks after the initial therapy, and under the random allocation, 50 U of botulinum toxin were injected into the left axilla previously injected with botulinum toxin and hyaluronic acid. The hyaluronic acid concentration was increased in this second injection, with 10%

Table 1. Change in Sweat Levels With Treatment (Either Botulinum Toxin Alone or Admixed With Hyaluronidase)

Patient	Botulinum	Botulinum and Hyaluronidase	Change in Sweat Test Before and After Treatment (mg per 5 minutes)	
			Botulinum and Hyaluronidase	Botulinum
2	10 U right axilla	10 U left axilla	148 mg (160 to 12)	153 mg (163 to 10)
3	50 U right axilla	50 U left axilla	148 (143 to less than 1)	28 (28 to less than 1)
4	25 U right axilla	25 U left axilla	367 (389 to 22)	433 (503 to 70)
	50 U left axilla	25 U right axilla	70 (70 to less than 1)	22 (22 to less than 1)
5	50 U left axilla	25 U right axilla	83 (83 to less than 1)	127 (127 to less than 1)
6	50 U right axilla	25 U left axilla	400 (410 to 10)	432 (432 to 0)

**Figure 2.** Patient 3 before and 2 weeks after injection of 50 U of botulinum toxin with hyaluronic acid into the right axilla.

hyaluronic acid being added rather than 4% as in the initial injection. This produced virtual anhidrosis of 10 mg per 5 minutes in this axilla. The right side previously injected with botulinum toxin became anhidrotic totally after injection with a further 25 U of botulinum toxin with added hyaluronic acid.

Patients 5 and 6 were allocated to receive 25 U (2.5 mL) of the combination botulinum toxin and

hyaluronidase in one axilla and 50 U of botulinum toxin (2.5 mL) in the other axilla.

Patient 5 had a decrease of 83 mg of sweat in his right axilla (botulinum toxin and hyaluronidase 25 U) and 127 mg of sweat in his left axilla (botulinum toxin 50 U) to anhidrotic levels (less than 1 mg of sweat per 5 minutes).

Patient 6 had a decrease of 400 mg of sweat in his left axilla (botulinum toxin and hyaluronidase 25 U) from 410 mg per minutes to 10 mg and a decrease of 432 mg of sweat in his right axilla (botulinum toxin 50 U) from 432 mg per 5 minutes to 0. His Minor's iodine test is illustrated in Figure 3.

Adverse Reactions

Patient 2 felt nonspecifically unwell 2 hours after receiving therapy and was rechallenged with skin testing and further injection without significant incident. No other reactions were noted.

Discussion

As discussed in the introduction, this pilot study aims to confirm the efficacy botulinum toxin admixed with hyaluronidase and if the mixture remains potent then to test whether hyaluronidase can increase the spread of botulinum toxin. The first patient illustrated both the retained efficacy of botulinum with added hyaluronidase and at least suggested that the effects may be spread by its use as the diffusion ring appeared to be substantially increased on the hyaluronidase-treated side. It was also hoped that the second patient would illustrate the spread of botulinum, but her gravimetric testing showed substantial improvement on both sides.

The central reason for conducting the study into hyaluronic acid is the intention of decreasing the recurrent costs of botulinum injections for hyperhidrosis patients. First, this is important, as these patients require large doses, and although studies have shown a dose related remission time in their sweating, most patients cannot afford higher and higher doses of

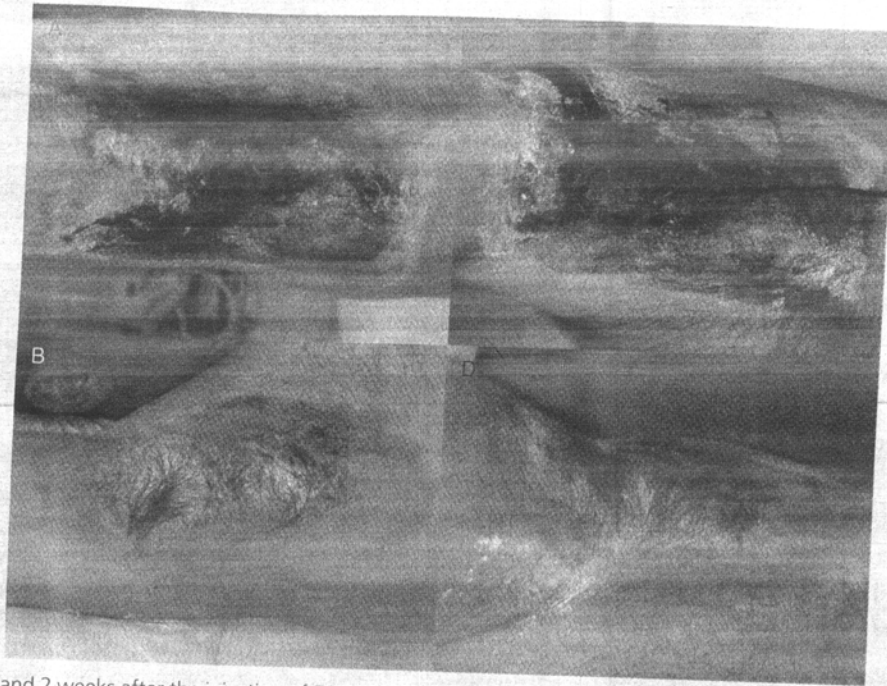


Figure 3. Patient 6 before and 2 weeks after the injection of 50 U of botulinum toxin into the right axilla (A and B) and after 25 U of botulinum toxin with 25 U of hyaluronidase into the left axilla (C and D).

botulinum in order to achieve satisfactory remission times. Also, health insurers, both government and private, are more likely to look to subsidizing and insuring a technology that is competitive in pricing to other available technologies, notably surgical ones. Thus, the dose of botulinum needs to be decreased preferably without sacrificing remission intervals. The hypothesis behind this trial is that it may be that the early recurrence with smaller doses of botulinum as against bigger doses is due to the relative paucity of agent at the limits of the diffusion of the overlapping injection zones, and that this may be improved by a more even spread of the agent afforded to it by the addition of botulinum. Thus, we may be able to replace a 50-U standard axillary injection of botulinum with a 25-U injection of botulinum with super-added hyaluronic acid.

Patient 3 illustrated that 50 U with and without hyaluronic acid certainly was effective. Patient 4, 5, and 6 are more important as we move into exploring the central tenet of a decreased dose of botulinum being achievable. Patient 4 was initially given a dose that for a reasonably heavily sweating male would usually be less than adequate; 25 U were injected into each axilla and gave predictably less than anhidrotic results, although the hyaluronidase side fared a little better, bringing the sweating rate down to 22 mg from 503 mg per 5 minutes versus the botulinum-treated side decreasing the sweat rate from 503 to 70 mg per 5 minutes (Table 1). After reversing the injections using

50 U of botulinum to the side previously injected with botulinum with hyaluronidase and 25 U of botulinum with hyaluronidase to the side previously injected with botulinum alone, predictably anhidrosis was achieved.

Patients 5 and 6 showed essentially similar findings, with anhidrosis being equally attained with half of the dose of botulinum toxin used when hyaluronidase was added. Patient 5 became anhidrotic on both sides after botulinum toxin 50 U in the right axilla and 25 U botulinum toxin with hyaluronidase but did not such a heavy perspiration load compared with patient 4.

Patient 6 suffered from considerable hyperhidrosis and became again virtually anhidrotic from both 25 mg of the combination botulinum toxin and hyaluronidase as well as from 50 U of the botulinum toxin alone.

These results suggest that (1) botulinum toxin is not substantially clinically altered in the short term by hyaluronic acid, (2) hyaluronic acid may increase the spread of botulinum toxin, and (3) hyaluronic acid may allow a decrease in the dose of botulinum toxin (at least in this short-term study) in the treatment of hyperhidrosis axillaris.

This study should be accepted for what it is: a short-term pilot study to establish whether further study is indicated. Further work will be required to establish whether longevity is maintained at lower doses and whether other areas and conditions traditionally treated with botulinum toxin may benefit from the use of hyaluronic acid.

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Commentary

Dr. Goodman continues to challenge our ideas! We have tended to follow the dilution/reconstitution and usage instructions initially formulated by Alan Scott and more recently by Allergan, Inc., the manufacturers of Botox. Dr. Goodman has challenged those by mixing hyaluronidase with BTX-A. He has questioned whether we need to be as careful about what we reconstitute with, and more importantly, he has queried our attitude and knowledge about diffusion. Is diffusion good or

bad? The answer is likely that it depends on a variety of factors such as the area, the dilution, and the dose. There is much that we still do not know about the clinical effects of BTX and its significance, and Dr. Goodman has reminded us of this. We shall find out more about the effects of admixing hyaluronidase in the future.

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