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ORIGINAL PAPER

Treatment of palmar hyperhidrosis with botulinum toxin type A: results of a pilot study based on a novel injective approach

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Abstract Botulinum toxin type A (BoNT/A) improves symptoms of palmar hyperhidrosis, but some drawbacks related to its injection in the hands still persist (e.g., muscle weakness caused by drug diffusion, pain during injections, or delayed functional recovery of the hand when using wrist block). In this open, controlled, non-randomized, intra-individual clinical trial, 50 patients with severe palmar hyperhidrosis received in the same session intradermal injections of BoNT/A through a new injection technique (NA/BoNT/A) based on the use of a specific adapter for needles (PCT/IT2011/000299) in one hand, and BoNT/A injection following the anaesthetic block of the wrist (WB/BoNT/A) in the other. Several measures of efficacy and safety were evaluated both before (T0) and four weeks after the treatment (T4): disease severity improvement, sweat reduction, handgrip strength decrease, pain/discomfort during the treatment, and patient's global satisfaction. All patients were also re-evaluated through the gravimetric assessment of sweat production in both hands at T12 and T24 to compare the long-term efficacy of the two treatments. All patients were responsive to the treatments, and disease severity was significantly decreased at T4 compared to baseline ($p < 0.0001$). Both procedures were equally effective in reducing sweat production in the short term ($p = 0.08$ at T4), but WB/BoNT/A caused a higher decrease of handgrip strength compared with WB/BoNT/A at T4 ($p < 0.0001$). Finally, patients reported that NA/BoNT/A and WB/BoNT/A procedures were comparable for pain/discomfort ($p = 0.204$); however, they were globally more satisfied with the NA/BoNT/A rather than WB/BoNT/A method ($p < 0.0001$). No significant difference in percentage of clinical relapse at T12 and T24 was detected between hands treated via WB/BoNT/A or NA/BoNT/A ($p = 0.70$). The use of the described adapter to inject BoNT/A in the hands seems to lead the clinicians to obtain same therapeutic results of conventional method based on the use of anaesthetic block of the wrist. Moreover, this new injective approach seems to increase the safety of the treatment by reducing the extent of muscle weakness and is preferred by patients mostly because it makes the functional recovery of the hand faster.

Keywords Palmo-plantar hyperhidrosis · Botulinum toxin A · Wrist block · Medical device

Introduction

Botulinum toxin type A (BoNT/A) has be successfully used for the management of patients suffering from palmar hyperhidrosis [9, 11, 14, 17–19, 21, 23, 25, 27, 29, 33], but two factors are still limiting its application for treatment of the hands: the discomfort related to the injections of BoNT/A in the palms and the handgrip strength reduction following the diffusion of BoNT/A towards the underlying muscle fibres.

To address these unmet medical needs, in this study we evaluated both efficacy and safety of BoNT/A administration by a new technique of injection based on the use of a specific needle adapter (NA/BoNT/A), which could be promising to optimize treatment of palmar hyperhidrosis with BoNT/A.

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This new approach to injecting BoNT/A was compared to conventional treatment based on the use of anaesthetic wrist block followed by BoNT/A Injection (WB/BoNT/A), to evaluate differences in short- (4 weeks) and long-term (24 weeks) efficacy and safety.

We analysed and compared the following measures of efficacy and safety: disease severity improvement, pain/discomfort during the treatment, handgrip strength decrease, sweat reduction, and patient's global satisfaction with the treatment.

Materials and methods

Design of the study

This pilot study (24 weeks long) has a clinical, open, controlled, non-randomized intra-individual design.

It was approved by the Polytechnic Marche University Ethical Committee, and conducted in accordance with the Declaration of Helsinski.

Population

Fifty patients (29 female and 21 male, mean age 38.2 ± 8.12) suffering from idiopathic severe palmar hyperhidrosis were included in the study.

Severe palmar hyperhidrosis was defined as follows: baseline Hyperhidrosis Disease Severity Scale score of 3 or 4 and baseline gravimetric measurement of spontaneous resting sweat production of at least 0.15 g/5 min/hand.

All included patients were resistant to any prior topical treatment (antiperspirants containing aluminium chloride, iontophoresis), and referred to our observation between January and February 2011. Ethical committee approval was obtained and all patients provided informed consent.

Patients were excluded from the study if they were pregnant or nursing women, had secondary hyperhidrosis or neuromuscular changes, or they were using systemic medications that might interfere with neuromuscular activity. All the enrolled patients showed a BMI within the range of normality. The dominant hand was the right for all the included patients.

Protocol of the study

Enrolled patients were evaluated at baseline (T0) for the following clinical parameters: Hyperhidrosis Disease Severity Scale (HDSS) [26], the gripping strength of both the hands (dynamic test with sphygmomanometer), and sweat production in both palms (gravimetric measurement). Each patient received the treatment with BoNT/A via needle adapter in one palm (NA/BoNT/A) and via wrist block (WB/BoNT/A) in the contralateral, simultaneously (T0).

The dominant hand is usually 10 % stronger than the nondominant hand (different studies range from 1 to 10 % difference) [22]; thus to avoid any bias in evaluation of handgrip strength reduction after treatment, 25 patients received the treatment via NA/BoNT/A in the right hand first, and the other 25 patients in the left hand, accordingly. Patients were target and internal control at the same time, because they received both the treatments simultaneously and were asked to report related pain/discomfort immediately after both treatments (VAS of pain).

Patients were then revaluated at T4, to investigate disease severity (HDSS), sweat production (gravimetric measurements), handgrip strength (dynamic test with sphygmomanometer), and global satisfaction with the treatments (self-administered questionnaire).

The short-term efficacy of the two treatments was compared at T4, whereas the long-term efficacy was extrapolated through the analysis of disease-free survival for each treated hand using the gravimetric assessment at T12 and T24.

Treatment with BTX-A type A

All patients received BoNT/A treatment with a fixed dosage per cm^2. Lyophilized botulinum toxin type A (BOTOX®, Allergan, Irvine, California, USA) 100 mouse units (MU) was diluted in 5 mL sterile 0.9 % saline solution.

In the palm, a reference grid with square areas of 2.25 cm^2 was drawn; the intracutaneous injection of BoNT/A 0.10 mL (2MU) was given by the physician in the central part of each square. The same dose was injected in every phalanx for the treatment of the fingers. The injections were made using a $30G \times 0.30 \times 4$ mm gauge needle, which was not replaced during treatment.

Thus, the total injected dose of BoNT/A per hand ranged from 100 to 150 MU, depending on the size of the hands.

Adapter for needle (NA)

The adapter was developed by a company specializing in production of prototypes, named ITACA s.r.l. of the Engineer Hagglund Gail. This medical device (Patent: PCT/IT2011/000299) was made of a high-strength, non-toxic, non-pyrogenic plastic polymer and it was repeatedly steamable in autoclave.

It was formed by two coupled bodies which, sliding on each other, allow varying the lengths of the needle's protrusion to control its depth of penetration through a graduated scale (Fig. 1). The medical device was used in 25 patients receiving BoNT/A on the right hand and in 25 patients on the left. It allows the injection of BoNT/A at a

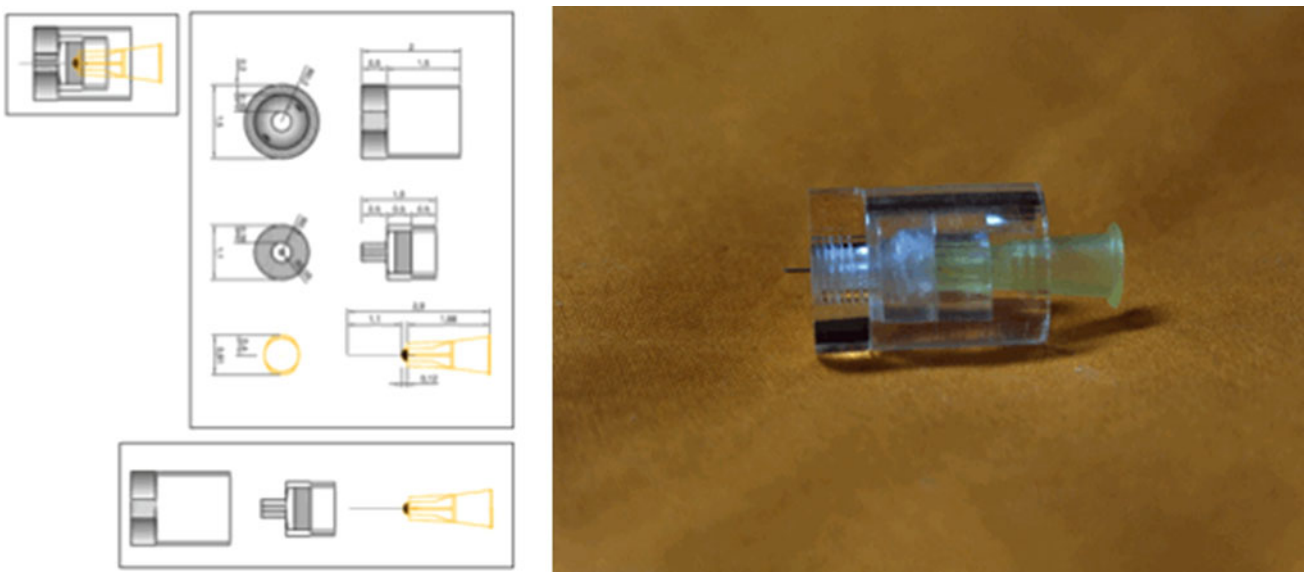

Fig. 1 Needle adapter for BoNT/A treatment (NA/BoNT/A treatment)

fixed depth ranging from 2.5 to 4 mm, according to the thickness of patients' epidermis, through a 30G × 0.30 × 13 mm gauge needle, allowing the spacing of injections approximately 1.5 cm from each other.

Wrist block (WB)

The loco-regional block of both median and ulnar nerves was performed in 25 patients on the right hand and in 25 patients on the left. Two mL of lignocaine 2 %, per nerve, was injected at the wrist using a 25G × 0.50 × 13 mm gauge needle. Patients were asked to bend the wrist and put the thumb and the two last fingers together to make evident both the palmaris longus and the flexor carpi radialis tendons. The needle was then inserted perpendicularly to the skin between the palmaris longus tendon and the flexor carpi radialis tendon at the proximal flexion crease of the wrist. Blockage of this nerve made the radial side of the palmar surface of the hand insensitive. To block ulnar nerve, the patient was asked to actively bend the wrist to make the flexor carpi ulnaris tendon more prominent and the needle was then inserted perpendicularly to the skin between the tendon and the ulnar styloid process (to avoid the risk of intra-ulnar artery injection). This block anaesthetizes the cubital portion of the palm of the hand, the little finger, and the median half of the fifth finger [8, 29].

Hyperhidrosis severity

Patients were asked to quantify disease severity through the HDSS [26] both before (T0) and 4 weeks after the treatment of both hands (T4).

A score of 3 or 4 indicated severe hyperhidrosis, and a score of 1 or 2 indicated mild or moderate hyperhidrosis. A successful treatment was identified as an improvement from a score 4 or 3 to a score 2 or 1, since a one-point improvement in HDDS score is associated with a 50 % reduction in sweat production and a two-point improvement with an 80 % reduction, according to the Canadian Hyperhidrosis Advisory Committee [26].

Conversely, a clinical relapse for the treated hand was identified as an increase of spontaneous sweat production at rest higher than 0.15 g/5 min/hand.

The worsening of HDDS was not taken into consideration to address differences in disease-free survival for hands according to the treatment received, because this is an overall questionnaire focused on the global clinical condition of the patient.

Pain/discomfort related to the treatment

The patients were asked to quantify the pain or discomfort globally related to the treatments immediately after they received them (T0) through two visual analogue scales (VAS) of pain.

The questions formulated to the patients were the following: "How strong was the pain you felt in your right hand?" and "How strong was the pain you felt in your left hand?"

VAS was a horizontal line 100 mm in length, anchored by word descriptors at each hand. Patients marked on the line the point that they felt represents their perception of pain/discomfort during the treatments received.

Handgrip strength

The apparatus used to evaluate handgrip strength was an Aneroid type of adult sphygmomanometer (J.A. Preston, Inc., 60 page Road, Clifton, New Jersey, 27012), which measures force in units of mmHg. The sphygmomanometer cuff was evenly enrolled, forming a circumference of approximately 14 cm to conform to a normal functional hand position for grip. A rubber band was placed around each end of the cuff to hold it in position. The cuff was inflated to 20 mmHg, which was the starting position for measurement of each subject. Under the direction of the same clinician, all the patients performed handgrip strength in the dominant and nondominant hands both before and after treatment with BoNT/A.

A mean score was calculated from three measurement sessions occurring approximately 10 min apart. The mean score among three trials was recorded for data calculations. Extraneous variables were controlled by using the same room with an average temperature of 21 °C and approximately the same time of day. Each patient was encouraged not to do any strenuous activity with the upper extremity during the study. This protocol for measurement of handgrip strength was suggested by Hamilton et al. [12]. The test was performed both before (T0), and 4 weeks after the treatment of both hands (T4). The handgrip strength difference between T0 and T4 values detected in patients treated via NA/BoNT/A or WB/BoNT/A were compared.

Sweat production

Quantitative gravimetric measurement of sweat secretion was conducted with standardized filter paper (Melitta GmbH, Minden, Germany), which was preliminarily weighed on a high-precision laboratory scale (Sartorius, Hamburg, Germany, precision+ 0.5 mg). The paper was then inserted into the closed palm of the patients for exactly 5 min and weighed again, yielding the rate of sweat secretion in grams per 5 min. The test was performed both before (T0), and 4, 12, and 24 weeks after the treatment of both hands (T4–T12–T24). The differences between T0 and T4 values of sweat production detected in patients treated via NA/BoNT/A or WB/BoNT/A were compared. Patients were followed for sweat production through gravimetric test, performed at T12 and T24, to evaluate the percentage of clinical relapse in the treated hands.

Global satisfaction of the patients with the treatment

Patients were asked to quantify their satisfaction with the treatments received 4 weeks later (T4) as follows: 0 (not satisfied), 1 (mildly satisfied), 2 (moderately satisfied), 3 (satisfied), and 4 (very satisfied).

Patients were encouraged to report their opinions on the differences between the treatments received in relation to muscle weakness and sweat production by answering four simple questions: Which treatment do you prefer? Which treatment is more comfortable? Which treatment causes the greatest muscle weakness? Which method allows a faster functional recovery of the hand?

Statistical analyses

GraphPad Prism version 6.00 for Mac, GraphPad Software, La Jolla California USA (www.graphpad.com) was used to perform all statistical analyses. All data were continuous variables expressed as mean ± SD. The normal distribution of continuous variables was verified with Kolmogorov–Smirnov test. Homogeneity of variance was tested by Cochran C, disease-free survival analysis was performed, and post hoc comparison with a nonparametric test (Mann–Whitney U test) was used to discriminate between means of values. Levels of significance were set at $p < 0.05$.

Results

All patients completed the study. Every patient had one hand treated via NA/BoNT/A and the other treated via WB/BoNT/A. 25 patients received the treatment via NA in the right hand and 25 in the left hand (ratio 1:1).

All patients were responsive to the treatments reporting a two-point improvement of HDSS, and HDSS mean values ± DS dramatically decreased from baseline (3.680 ± 0.4712) to T4 (1.360 ± 3.484) in all treated patients ($p < 0.0001$) (Fig. 2).

The two injection procedures were equally effective in reducing sweat production at T4 (mean sweat production decreased from a baseline value of 0.1562 ± 0.004 to a

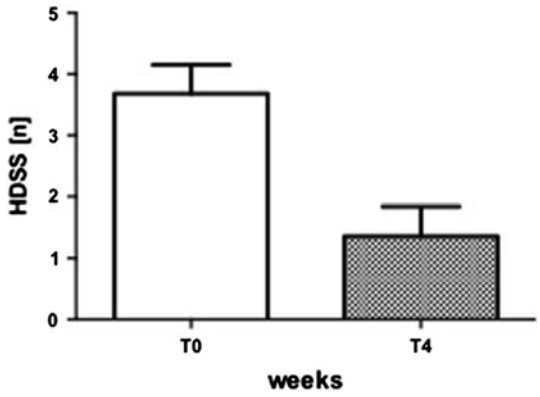

Fig. 2 The median HDSS score dramatically decreased from baseline to T4 values independent of the method used for BoNT/A administration ($p < 0.0001$)

post-treatment value of 0.10 ± 0.02 in hands treated via NA/BoNT/A, and from a baseline value of 0.1552 ± 0.003 in hands treated via WB/BoNT/A (Fig. 3).

The disease-free survival analysis demonstrated that the percentage of relapse between hands treated via NA/BoNT/A was similar to that reported for hands treated via WB/BoNT/A (Fig. 4).

In all patients handgrip strength reduction occurred, but hands treated via WB/BoNT/A had a stronger decrease of handgrip strength compared to hands that received NA/BoNT/A. Mean strength of hands treated via NA/BoNT/A was reduced from a baseline value of 130.4 ± 12.85 mmHg to a post-treatment value of 105.6 ± 16.78; hands treated via WB/BoNT/A reported a reduction in strength from a baseline value of 128.5 ± 11.08 mmHg to a post-treatment value of 88.96 ± 17.50 (Fig. 5).

Patients judged that the NA/BoNT/A was as uncomfortable as the WB/BoNT/A method (VAS mean value ± SD in patients treated via NA: 5 ± 1.602 mm; VAS mean ± SD in patients treated via conventional method: 4.5 ± 2.97 mm, $p = 0.204$) (Fig. 6), but globally preferred it (patients' satisfaction with NA method mean value ± SD 2.420 ± 0.702; patients' satisfaction with conventional method with WB mean value ± SD 1.820 ± 0.719, $p < 0.0001$) (Fig. 7).

All patients (50/50) reported that, according to their opinion, the NA/BoNT/A procedure was as effective as WB/BoNT/A, but preferred the first because it allowed the functional recovery of the hand faster.

Most of them (47/50) stated that the transient weakness of the hand induced by the treatment was perceived less intense with the NA/BoNT/A procedure.

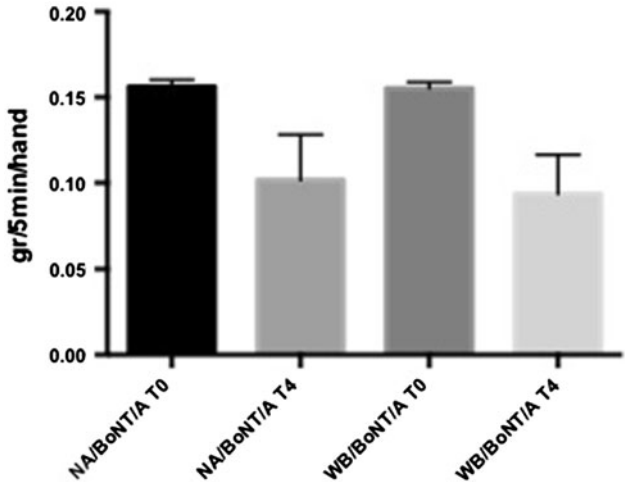

Fig. 3 The NA/BoNT/A and the WB/BoNT/A procedures were equally effective in reducing sweat production after 4 weeks of treatment (NA/BoNT/A T0 vs. NA/BoNT/A T4 $p < 0.0001$; WB/BoNT/A T0 vs. WB/BoNT/A T4 $p < 0.0001$; NA/BoNT/A T0 vs. WB/BoNT/A T0 $p = 0.22$; NA/BoNT/A T4 vs. WB/BoNT/A T4 $p = 0.08$)

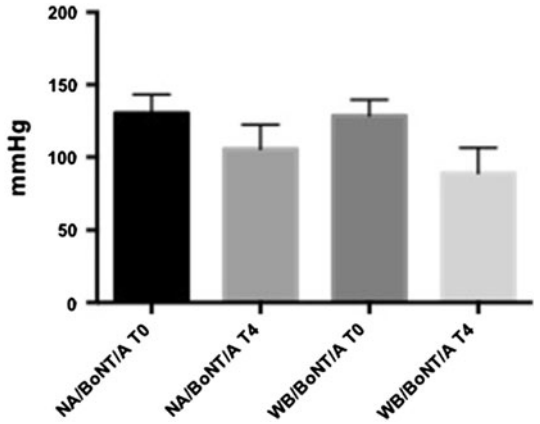

Fig. 5 The WB/BoNT/A resulted in a higher decrease of handgrip strength compared to the NA/BoNT/A procedure after 4 weeks of treatment ($p < 0.0001$). (NA/BoNT/A T0 vs. NA/BoNT/A T4 $p < 0.0001$; WB/BoNT/A T0 vs. WB/BoNT/A T4 $p < 0.0001$; NA/BoNT/A T0 vs. WB/BoNT/A T0 $p = 0.50$; NA/BoNT/A T4 vs. WB/BoNT/A T4 $p < 0.0001$)

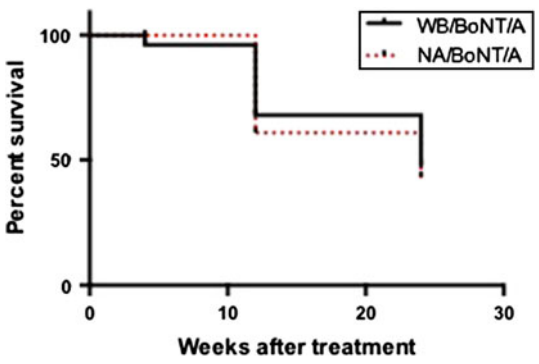

Fig. 4 The percentage of disease-free survival in hands treated via NA/BoNT/A was similar to that reported in hand treated via WB/BoNT/A

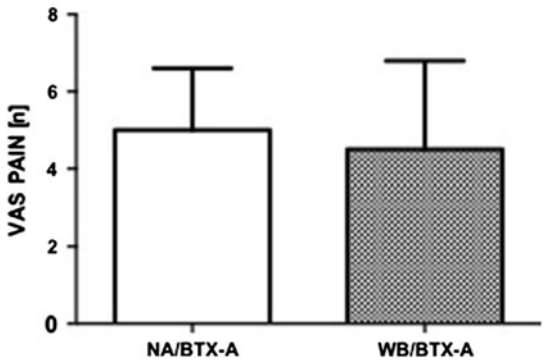

Fig. 6 NA/BoNT/A and WB/BoNT/A treatments were equally tolerated by the patients ($p = 0.204$)

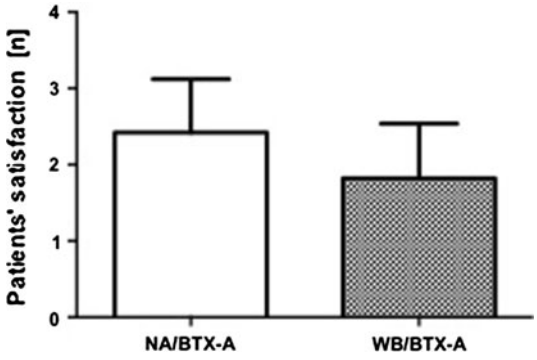

Fig. 7 Patients preferred the NA/BoNT/A procedure to the WB/BoNT/A procedure ($p < 0.0001$)

Discussion

Recently, a consumer survey of a nationally representative sample of 150,000 households in the USA screened for the presence of hyperhidrosis [16].

A German study [13] reported that the prevalence of PPH among hyperhidrotic patients was 66.7 % and a French study reported 51 % [3].

PPH actually affects more people than previously thought. Several studies [10–30] have demonstrated that BoNT/A is safe and effective for the treatment of axillary hyperhidrosis (level A evidence); however, less data are available on the efficacy and safety of BoNT/A in the treatment of PPH (level B evidence) [3, 6]. Two main factors that limit the use of BoNT/A in the treatment of PPH are: pain during the injection of the drug and development of handgrip weakness related to diffusion of BoNT/A to the underlying hand muscles.

The series of injections through the densely innervated skin of the palms is often rated as very painful, even if topical anaesthetic cream, ethyl chloride liquid spray and/or cold packs are applied [17–19, 23, 25, 27, 29]. Intravenous regional anaesthesia (Bier's block) [4, 5] seems to be effective, but requires assistance from an anaesthesiologist. For this reason, the use of loco-regional anaesthesia of the median and ulnar nerves before the treatment is often used [7, 8, 15, 18–20, 29], and the wrist block still remains the gold standard among the analgesic procedures for BoNT/A injection. However, blockage of the ulnar and median nerves at the wrist can be associated with a risk of mechanical and chemical neural damage [7, 12] as a result of the deep injection of anaesthetic, and is not a common medical procedure. It could also be inferred that a subcutaneous injection of BoNT/A is more tolerable [25]; however, intracutaneous administration is the most appropriate procedure for palmar hyperhidrosis to deliver the toxin as close to the sweat glands as possible.

The identification of an optimal dilution of BoNT/A radically decreased the incidence of transient muscle weakness related to drug diffusion towards the underlying muscles of the hands, but did not abolish the risk of an excessive deep injection of BoNT/A, which is operator dependent.

Recently, novel needle-free injection devices have been developed and used to minimize needlestick injuries: examples are the MED-JET®, the Dermojet® and the MadaJet XL®. The first is a relatively low-pressure device that injects directly lidocaine with an adjustable range of volumes (0.01–0.3 mL) through a small orifice forming a subepidermal wheal which allows subsequently the introduction of BTX-A with needle in a painless way.

This device is very expensive ($5,000 for unit in USA) and requires the use of the anaesthetic, which our device allows to avoid.

The Dermojet® and the MadaJet XL® are devices similar to MED-JET® but they have a fixed volume per spurt, which is 0.1 mL.

Since for increased volume per spurt, the injection reaches an increased penetration depth, injury to superficial palmar nerves or vessels and weakness of the muscles of the hand cannot be excluded. So the Dermojet® and the MadaJet XL® are not suitable for the treatment of palmar hyperhidrosis [1–32].

The NA medical device described in this study matches the two factors limiting the use of BoNT/A in the treatment of PPH.

Firstly, it seems to be able to reduce the pain due to injections: patients reported that the perceived discomfort with the BoNT/A procedure, which does not include any anaesthesia, was similar to that experienced with conventional method based on WB, probably because the WB is itself a somewhat uncomfortable procedure and does not provide any analgesia in areas of the hand innervated by the radial nerve.

Secondly, the new injection procedure could reduce the risk of releasing BoNT/A too deep, since it allows administering BoNT/A at a measurable depth of 2.5 mm. Recently, a dynamic analysis of eccrine sweat glands on human fingertips, by optical coherence tomography, demonstrated that the medium scanning depth of sweat glands is also 2.5 mm in humans [13]. It follows that the use of the described NA medical device could allow even less experienced clinicians to release BoNT/A at the optimal depth to treat hyperhidrosis and to avoid intramuscular injection.

Although literature discloses that oblique injections reduce the risk of backflow of botulinum toxin from the injection site preserving the effectiveness of injections, in our study, using perpendicular injections, we did not find significant differences in efficacy between the two techniques [9].

Finally, patients seem to be more satisfied with the treatment based on the use of NA, compared to

conventional method based on WB, because it is associated with a faster functional recovery of the hand and a less perceived muscle weakness.

Although further long-term studies are needed, our preliminary results seem to be promising: this medical device is as effective as the conventional method based on the use of wrist block, both in short and long term; moreover, it could reduce the risks and increase patient's compliance to the treatment of palmar hyperhidrosis with BoNT/A.

Conflict of interest The authors declare that they have no conflict of interest.

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