

# Iontoforese de Toxina Botulínica Tipo A na Hiperidrose Palmar

## *Botulinum Toxin Type A Iontophoresis in Palmar Hyperhidrosis*

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### Resumo

**Introdução:** O aperto de mão é uma forma de interação com os que nos rodeiam e pode ser limitado pela hiperidrose palmar, uma doença que tem grande impacto nas relações afetivas, laborais e sociais. Este estudo tem como objetivo rever as evidências existentes sobre a eficácia da toxina botulínica tipo A no tratamento *off-label* da hiperidrose palmar e consequente impacto na qualidade de vida, e também o papel da iontoforese como método de administração da toxina.

**Material e Métodos:** A expressão “botulinum toxin” AND “palmar hyperhidrosis” AND (“quality of life” OR “iontophoresis”)” foi pesquisada nas bases de dados eletrónicas PubMed, Cochrane e PEDro.

**Resultados:** A toxina botulínica tipo A, apesar do seu custo e efeito terapêutico transitório, é uma opção válida no tratamento de doentes com sudorese severa que não respondem aos tratamentos tópicos. Os benefícios da utilização da toxina botulínica tipo A para reduzir a hiperidrose palmar foram documentados em diversos estudos, sendo relatada uma melhoria significativa na qualidade de vida após o tratamento. A injeção palmar de toxina botulínica é no entanto muito dolorosa. Estudos anteriores demonstraram que a toxina botulínica tipo A pode ser eficazmente administrada nas palmas das mãos por iontoforese com um impacto favorável na qualidade de vida.

**Conclusões:** A hiperidrose palmar, pode originar situações sociais e profissionais constrangedoras, bem como ter um impacto psicológico sobre os doentes afetados. A injeção de toxina botulínica tipo A reduz a produção de suor nas mãos, mas este procedimento tem limitações. A toxina botulínica tipo A administrada por iontoforese alia uma técnica não invasiva e barata a uma opção terapêutica segura e eficaz no tratamento da hiperidrose palmar.

A toxina botulínica tipo A, mesmo quando administrada por iontoforese, é uma opção de tratamento eficaz para a hiperidrose palmar e esse facto reflete-se positivamente na qualidade de vida dos doentes. Considerando as evidências estabelecidas, é importante rever esta utilização *off-label*.

**Palavras-chave:** Hiperidrose; Toxina Botulínica Tipo A; Iontoforese; Qualidade de Vida.

### Abstract

**Introduction:** Handshake is a form of interaction with those around us and it may be limited by palmar hyperhidrosis, a disease that has substantial impact upon affective, workplace and social relationships. This study aims to review the existing evidences about the effectiveness of botulinum toxin in the off-label treatment of palmar hyperhidrosis and consequent impact on quality of life, and also the role of iontophoresis as a drug delivery method.

**Material and Methods:** The expression “botulinum toxin” AND “palmar hyperhidrosis” AND (“quality of life” OR “iontophoresis”)” was searched on PubMed, Cochrane and PEDro databases.

**Results:** Botulinum toxin type A, despite its cost and the transient therapeutic effect, is a valid treatment option

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*in patients with severe sweating who have not responded to topical treatments. The benefits of using botulinum toxin type A to reduce palmar hyperhidrosis were documented in several studies and it was reported a significant improvement on quality of life after treatment. Palmar injection of botulinum toxin is however very painful. Previous studies demonstrated that botulinum toxin type A can be effectively delivered to the palms by iontophoresis with a favorable impact on quality of life.*

**Conclusions:** *Palmar hyperhidrosis can lead to embarrassing social and occupational situations as well as have a psychological impact on the patients affected. Botulinum toxin type A injection grants the reduction of sweat production on hands, but this procedure has limitations. Botulinum toxin type A iontophoresis combines a non-invasive and inexpensive delivery method with a safe and effective treatment option for palmar hyperhidrosis.*

*Botulinum toxin type A, even when delivered by iontophoresis, is an effective treatment option for palmar hyperhidrosis and that fact reflects positively on patients' quality of life. Considering the established evidences, it is important to revise this unlabeled use.*

**Keywords:** *Botulinum Toxins, Type A; Hand; Hyperhidrosis; Iontophoresis; Quality of Life.*

## Introduction

Our life implies constant interaction with those around us, whether in the family, work or social context. Handshake is a form of greeting and can also symbolize an agreement between two parties; this simple act may be limited by some diseases (e.g. palmar hyperhidrosis) that impair the performance of daily life activities and, ultimately, the quality of life.

Hyperhidrosis results from sympathetic hyperactivity of the eccrine sweat glands; it can be primary or secondary and of local or generalized distribution.<sup>1-3</sup> The most common type is primary focal hyperhidrosis (unknown cause) which tends to occur in areas with greater concentrations of eccrine glands (histological and numerically normal), such as palms.<sup>1,4,5</sup> This condition may affect up to 1-3% of the population and about half of patients report some family history; incidence is equal in both sexes.<sup>1,3-8</sup> Palmar hyperhidrosis is one of the most debilitating types of hyperhidrosis, particularly problematic as it has substantial impact upon affective, workplace and social relationships in affected individuals; in extreme cases, it can result in social isolation or occupational disability.<sup>1,4,8,9</sup>

Botulinum toxin is one of the most potent neurotoxins; there are eight serotypes.<sup>10</sup> Most clinical applications are based on its ability to block neuromuscular transmission: it binds to the presynaptic cholinergic systems and prevents acetylcholine release promoting reversible muscle paralysis.<sup>8</sup> Botulinum toxin type A has precise indications, however there are some off-label uses described.<sup>11,12</sup> Administration of botulinum toxin is usually made by injection but there are other available options (e.g. iontophoresis).<sup>3,4</sup> This study aims to review the existing evidences about the effectiveness of botulinum toxin in the treatment of palmar hyperhidrosis and consequent impact on patients quality of life, and also the role of iontophoresis as a drug delivery method.

## Material and Methods

The expression “botulinum toxin” AND “palmar hyperhidrosis” AND (“quality of life” OR “iontophoresis”) was searched on PubMed, Cochrane and PEDro databases on 2013 August 1. Articles were elected for full text reading by abstract evaluation. When relevant, references from these articles were also checked.

## Results

Search retrieved 20 results and 12 articles were selected for further analysis (Table 1). Information gathered from the available literature is summarized below.

Palmar hyperhidrosis may occur in isolation or association; gravimetric measurements of palmar sweating - method used to document the magnitude of abnormal palmar sweating - show that patients with hyperhidrosis easily exceed 12 to 30 times normal rates of eccrine secretion from the palmar surface of the hands and fingers.<sup>1,13</sup> In most cases this excessive sweating is aggravated by emotional factors such as public speaking or meeting new social contacts at work/leisure, high ambient temperature, and/or ingestion of stimulants like coffee.<sup>13</sup>

Most conventional treatments for focal hyperhidrosis (e.g. topical aluminum chloride, oral anticholinergics, tap water iontophoresis, thoracic sympathectomy) are of limited effectiveness or may be associated with major side effects.<sup>1,3-6,9,14,15</sup> Botulinum toxin type A is a valid treatment option in patients with severe sweating (e.g.  $\geq 1$  mg/cm<sup>2</sup>/min) who have not responded to topical treatments, despite its cost and the transient therapeutic effect.<sup>3,8,16</sup>

Injection of botulinum toxin can effectively inhibit the release of acetylcholine from the presynaptic cholinergic nerve fibers, causing chemodenervation of the eccrine sweat glands and reduction of sweat

Table 1 – Articles selected for full reading.

Reference	Article
2	Lowe N, Campanati A, Bodokh I, Cliff S, Jaen P, Kreyden O, et al. The place of botulinum toxin type A in the treatment of focal hyperhidrosis. <i>Br J Dermatol.</i> 2004;151(6):1115-22.
5	Walling HW, Swick BL. Treatment options for hyperhidrosis. <i>Am J Clin Dermatol.</i> 2011;12(5):285-95.
6	Baumgartner FJ, Bertin S, Konecny J. Superiority of thoracoscopic sympathectomy over medical management for the palmoplantar subset of severe hyperhidrosis. <i>Ann Vasc Surg.</i> 2009;23(1):1-7.
9	Kavanagh GM, Shams K. Botulinum toxin type A by iontophoresis for primary palmar hyperhidrosis. <i>J Am Acad Dermatol.</i> 2006;55(5 Suppl):S115-7.
14	Davarian S, Kalantari KK, Rezasoltani A, Rahimi A. Effect and persistency of botulinum toxin iontophoresis in the treatment of palmar hyperhidrosis. <i>Australas J Dermatol.</i> 2008;49(2):75-9.
17	Campanati A, Sandroni L, Gesuita R, Giuliano A, Giuliadori K, Marconi B, et al. Treatment of focal idiopathic hyperhidrosis with Botulinum Toxin Type A: clinical predictive factors of relapse-free survival. <i>J Eur Acad Dermatol Venereol.</i> 2011;25(8):917-21.
20	Coutinho dos Santos LH, Gomes AM, Giraldo S, Abagge KT, Marinoni LP. Palmar hyperhidrosis: long-term follow-up of nine children and adolescents treated with botulinum toxin type A. <i>Pediatr Dermatol.</i> 2009;26(4):439-44.
21	Ambrogi V, Campione E, Mineo D, Paternò EJ, Pompeo E, Mineo TC. Bilateral thoracoscopic T2 to T3 sympathectomy versus botulinum injection in palmar hyperhidrosis. <i>Ann Thorac Surg.</i> 2009;88(1):238-45.
22	Pérez-Bernal AM, Avalos-Peralta P, Moreno-Ramírez D, Camacho F. Treatment of palmar hyperhidrosis with botulinum toxin type A: 44 months of experience. <i>J Cosmet Dermatol.</i> 2005;4(3):163-6.
26	Campanati A, Penna L, Guzzo T, Menotta L, Silvestri B, Lagalla G, et al. Quality-of-life assessment in patients with hyperhidrosis before and after treatment with botulinum toxin: results of an open-label study. <i>Clin Ther.</i> 2003;25(1):298-308.
27	Rosell K, Hymnelius K, Swartling C. Botulinum toxin type A and B improve quality of life in patients with axillary and palmar hyperhidrosis. <i>Acta Derm Venereol.</i> 2013;93(3):335-9.
32	Choi YH, Lee SJ, Kim do W, Lee WJ, Na GY. Open clinical trial for evaluation of efficacy and safety of a portable "dry-type" iontophoretic device in treatment of palmar hyperhidrosis. <i>Dermatol Surg.</i> 2013;39(4):578-83.

production (glands luminal area often decreases); therapeutic effect duration is not significantly influenced by age, sex or extension of hyperhidrotic area.<sup>9,14,17,18</sup>

The benefits of using botulinum toxin type A to inhibit palmar hyperhidrosis have been well documented in several studies: two double-blinded, randomized, placebo-controlled studies have shown that this treatment is safe and can control hyperhidrosis for 3-5 months, despite there is a definitive range of responses to treatment varying from about 3 to 16 months.<sup>2,13,18-24</sup> Another positive point is that compensatory sweating linked to sympathectomy has not been reported in focal chemodenervation with botulinum toxin.<sup>13,15,21,25</sup> Many studies have reported a significant improvement on patients' quality of life after treatment with botulinum toxin type A based on some scales (e.g. Hyperhidrosis Disease Severity Scale, Dermatology Life Quality Index, Hyperhidrosis Impact Questionnaire).<sup>2,8,20,21,26,27</sup>

However, palmar injection of botulinum toxin is very painful and may cause transient weakness of the adjacent small muscles of the hand (inaccurate targeting or diffusion of botulinum toxin to nearby muscles): few people can tolerate the discomfort of some dozen needle sticks per palm without anesthesia, so most patients require some kind of it (e.g. local anaesthesia, cryoanalgesia, regional nerve block, hypnosis) prior to undergoing palmar injection; many patients develop a transient period of weakness and instability of the lumbrical muscles of the hand so that simple tasks such as opening a stuck lock with a key or shoving a button through a tight button hold may become difficult during some days after treatment and can remain so for one month.<sup>3,9,13,14,18,22,24,28,29</sup>

For those reasons some authors investigated the hypothesis of a non-invasive treatment considering that topically-administered botulinum toxin type A can reach target eccrine glands via sweat pores and that the palmar glabrous skin has the highest density

of sweat pores.<sup>4</sup> Theoretically, pore size and osmotic gradient would be directly proportional to rate of absorption of topically-administered botulinum toxin, whereas size of the molecule would bear an inverse relationship; application of an electrical gradient (iontophoresis) or low-frequency ultrasound (sonophoresis) could also positively influence transport of botulinum toxin into the sweat glands.<sup>3,4</sup>

Previous studies (including a small, double-blind, randomized, placebo-controlled study) demonstrated that a non-ionic drug such as botulinum toxin type A can be effectively and painlessly delivered to the palms by iontophoresis.<sup>9</sup> Botulinum toxin iontophoresis reduces palmar sweating by up to 81%, and this effect lasts some 3 months; no side effects have been reported.<sup>7,9,14</sup> This technique reduces the sweating more quickly than iontophoresis of normal saline and the dryness lasts longer; besides that, the dry area exceeds the location covered by the active electrode but, unlike injections, botulinum toxin iontophoresis does not decrease either intrinsic or extrinsic hand muscle strength.<sup>9,14</sup> A favorable impact is also seen on patients' quality of life.<sup>14</sup>

Because of the experimental basis of the few existing studies, botulinum toxin iontophoresis was applied once, except in one patient that received a second treatment after 3 months because sweating recurrence.<sup>3,7,9,14</sup> Most authors used 100 IU (Botox®) diluted in 1.5 to 3 mL of preservative-free saline, treated seven to nine sites on the patient's palm, approximately 3 cm apart, with circular drug-delivery reservoirs covering 0.64 cm<sup>2</sup> each one and an electrical charge of 0.4 mA to the highest comfortable current (total dosage of 15.0 mAmin).<sup>3,7,9</sup>

## Discussion

Palmar hyperhidrosis can lead to embarrassing social and occupational situations as well as have a psychological impact on the patients affected.<sup>5</sup> Many patients cover this affliction by resorting to elaborate behavior rituals, such as repetitively wiping their palms on clothes, carrying towels and handkerchiefs at all times, and avoiding the dreaded handshaking at all costs.<sup>13</sup> Focal hyperhidrosis is a benign, socially rather than medically, burdensome condition associated with a decreased quality of life.<sup>2,4,27</sup> Botulinum toxin type A injection grants the reduction of sweat production on hands and this fact improves patients' quality of life with benefit for interpersonal relationships in all environments; despite that, the procedure has its limitations.

Theoretically, topical administration of botulinum toxin can be unassisted or assisted; assisted techniques of application of botulinum toxin may

include the application of a small electrical current or low-frequency ultrasound.<sup>4,30</sup> Iontophoresis is a drug delivery system that uses a small external electric current to deliver water-soluble, charged drugs into the skin.<sup>7</sup> The requirements for a drug to be delivered by iontophoresis include solubility in water, polarity and a suitable molecule size.<sup>7</sup> As well as increasing solvent flow, the process actually appeared to increase pore size, and possibly induced new pore formation in the skin.<sup>7,30</sup> The amount of drug delivered by iontophoresis is directly proportional to the total electrical charge applied, drug concentration and total dose.<sup>7</sup> The botulinum toxin complex is negative at neutral pH and was clearly detected in association with cutaneous striated skeletal muscle fibers localized in the deep dermis of rats after iontophoresis; as far as the animal model is concerned, for practical and legal purposes it is assumed that human skin absorption is equal to rat in vivo dermal absorption.<sup>7,31</sup> Hair and adnexa represent a preferential pathway for molecules undergoing iontophoresis through mammal skin.<sup>31</sup> Botulinum toxin type A iontophoresis combines a non-invasive and inexpensive delivery method with a safe and effective treatment option for palmar hyperhidrosis with benefits on quality of life.<sup>3</sup>

Some investigators postulate that botulinum toxin can be administered topically without assistance (e.g. immersing the hand in a shallow container of botulinum toxin reconstituted in normal saline; using tight-fitting powder-free plastic gloves after the same solution have been carefully squirted into the palmar glove side along the inside of the sleeve and the wrist tied off to prevent leakage), but Chow A and Wilder-Smith EP failed to show an effect of a simple transdermal application method of botulinum toxin in the treatment of palmar hyperhidrosis.<sup>4,30</sup> Factors that are likely to influence the success of this method of administration include concentration, temperature of the solution and size of the sweat pores (in order to ensure large sweat pore size, it may be necessary to warm the surface of the palm first (e.g. with a heat lamp)).<sup>4,30</sup>

Considering the future, smaller molecules of botulinum toxin (even free of complexing proteins) may allow greater absorption of the toxin through the sweat pores.<sup>4,30</sup> It is possible that formulations containing only the light chain of botulinum toxin (the active component of the molecule) reconstituted in gel or cream form may be all that is required to treat palmar hyperhidrosis.<sup>4,30</sup> Recently, a new portable "dry-type" iontophoretic device for treatment of palmar hyperhidrosis was created; it uses the patient's sweat itself as a medium and patients grasps the device with the palm for 20 minutes once a day for 4 weeks with good results.<sup>32</sup> Why not try it for botulinum toxin topical administration?

## Conclusions

Botulinum toxin type A is not a curative therapy but, even when delivered by iontophoresis, is an effective treatment option for palmar hyperhidrosis and that fact reflects positively on patients' quality of life. Considering these established evidences it is important

to revise this unlabel use and empower investigation to grant this new indication. Further large trials will certainly shed light on the duration of anhidrotic effect, optimal dose, best delivery technique, side-effects and cost-effectiveness compared to conventional therapies.

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