World Journal of Neurology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5316/wjn.v3.i4.133

World J Neurol 2013 December 28; 3(4): 133-137
ISSN 2218-6212 (online)

MINIREVIEWS

Overview of botulinum toxin as a treatment for spasticity in stroke patients

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Received: June 26, 2013 Revised: October 3, 2013
Accepted: November 2, 2013
Published online: December 28, 2013

Abstract

Spasticity after the occurrence of stroke induces limb deformity, functional disability and/or pain in patients, which limits their activities of daily living and deteriorates their quality of life. Botulinum toxin (BTX) has recently been reported as an efficacious therapeutic agent for the treatment of spasticity. Systematic review and meta-analysis studies have demonstrated that BTX therapy after stroke reduces spasticity and increases physical activity capacity and performance levels. Moreover, BTX can be used as an adjuvant in physiotherapy. Several studies have confirmed that the combination of BTX therapy and physiotherapy improves motor recovery. However, to date, only a few such combination studies have been conducted and their findings are considered preliminary and controversial. Therefore, future studies are required to determine the appropriate combination of treatment methods that will aid motor recovery.

Key words: Botulinum toxin; Rehabilitation; Stroke; Spasticity; Neurorehabilitation

Core tip: In this overview, we describe that botulinum toxins (BTXs) were very useful to reduce spasticity in stroke patients. Moreover, we introduce studies on appropriate effective and safe injection methods; pilot studies that evaluated combined rehabilitation and BTX treatment; and adverse events after BTX injection, including risk factors of neutralizing antibodies.

Isoyama H, Takeuchi N. Overview of botulinum toxin as a treatment for spasticity in stroke patients. *World J Neurol* 2013; 3(4): 133-137 Available from: URL: http://www.wjgnet.com/2218-6212/full/v3/i4/133.htm DOI: http://dx.doi.org/10.5316/wjn.v3.i4.133

INTRODUCTION

Spasticity is a common complication in patients who have experienced stroke. The incidence of spasticity is reported to be 17%-43% in post-stroke patients[1-3]. Spasticity induces limb deformity, functional disability and/or pain that limits activities of daily living (ADL) and deteriorates the quality of life (QOL). In order to reduce spasticity, clinicians prescribe oral medications, intrathecal baclofen therapy, nerve phenolization, casting or splinting, rehabilitation therapy or a combination of these therapeutic approaches[4-8]. A recent study has shown that botulinum toxin (BTX) is an efficacious therapeutic agent for the treatment of spasticity[9].

BTX is poisonous in nature and is produced by the anaerobic bacterium *Clostridium Botulinum*[10]. BTX blocks vesicular acetylcholine release at neuromuscular junctions and reduces focal muscle tonus and contracture[11]. Therefore, BTX is used for treating muscular hyperactivity and excessive or inappropriate muscle contraction. Seven types of BTX exist in nature, but two toxin types, type A (BTX-A) and type B (BTX-B), are used in the clinical

setting. Most clinical trials have utilized BTX-A because it has a longer lasting effect than BTX-B[12,13]. BTX-B tends to be selected for spasticity treatment when patients have neutralizing antibodies against BTX-A or develop antibodies after repetitive BTX-A injection treatment[14,15].

Many studies have reported that BTX injection treatment reduces spasticity in stroke patients[16-25]. However, a few studies have focused on rehabilitation therapy after BTX treatment for improving motor function[26-28]. This review focuses on the following factors of BTX treatment in post-stroke patients: (1) the effectiveness of spasticity reduction, with regard to ADL and QOL; (2) the appropriate injection method; (3) combined BTX therapy and neurorehabilitation; and (4) adverse events. The purpose of this review is to provide a comprehensive overview of BTX treatment for muscular spasticity in post-stroke patients, to understand its mechanisms of action, and to suggest appropriate treatment approaches.

EFFECTIVENESS FOR SPASTICITY

Several reports clarified the effectiveness of BTX treatment for upper limb spasticity experienced after stroke[16-21]. A recent systematic review and meta-analysis reported that BTX-A reduced spasticity and thereby improved physical activity capacity and performance levels in the upper limb in patients who experienced stroke[29]. BTX-A (Botox®) injection in the upper limb muscles are recommended at the following doses: 25-100 units for the flexor carpi radialis; 20-70 units for the flexor carpi ulnaris; 20-60 units for the flexor digitorum superficialis; 20-60 units for the flexor digitorum profundus; 10-30 units for the flexor pollicis longus; and 5-25 units for the adductor pollicis[30].

Furthermore, several studies have reported the effectiveness of BTX therapy in stroke-induced lower limb spasticity[22-25]. However, a systematic review and meta-analysis reported that BTX-A treatment for stroke-induced lower limb spasticity was associated with a slight improvement in functional ambulation[19,31]. A multicenter, double-blind trial demonstrated the effectiveness of BTX-A in cases of lower limb spasticity, but improvements in gait pattern scale and speed were not significant, compared to that observed in the placebo group[32]. A previous study suggested that high-dose BTX-A treatment may induce excessive muscle weakening that may deteriorate limb function[25]. BTX-A (Botox®) injection doses in the lower limb is recommended at the following doses: 50-250 units for the medial and lateral head of the gastrocnemius respectively; 50-200 units for the soleus; and 50-150 units for the tibialis posterior[30]. However, to the best of our knowledge, no study has evaluated the appropriate BTX dose for treatment of upper and lower limb spasticity and therefore, future studies are required to clarify these dosages. Moreover, it is noted that clinicians should consider the maximum dose of BTX per session, which differs in each country (*e.g.,* 360 units in Japan and 600 units in Europe)[32-35].

Treatment of spasticity in patients who experience a stroke with BTX-A may improve ADL and QOL[36,37]. A previous study reported that high-dose BTX-A significantly improved ADL scores for limb position and self-dressing[36]. Furthermore, another study in post-stroke patients reported that BTX-A therapy improved overall QOL scores and muscle tone, reduced disability, and improved the ability to function[37]. However, a recent meta-analysis study revealed that BTX-A did not significantly improve overall health-related QOL[38].

APPROPRIATE INJECTION METHOD

Several studies have reported on BTX-A injection techniques[39-41]. Francisco *et al*[39] compared the efficacy of high and low volumes of BTX at the same dose for wrist and finger flexor spasticity. They found that modified Ashworth Scale scores were significantly decreased in both high and low-volume injection groups. However, there was no significant difference between the groups[40]. Gracies *et al*[41] reported that injecting a small volume of BTX-A near the neuromuscular junction was more effective than injecting a similar volume at a greater distance from the neuromuscular junction. However, injecting a large volume at a greater distance from the junction was as effective as a small volume injected near the neuromuscular junction. Mayer *et al*[40] also reported that a single motor point and multisite low-dose, high-volume BTX-A injections produced a similar impact in spasticity reduction. Therefore, the appropriate injection methods according to BTX-A volume and injection points must be elucidated. Moreover, BTX-A injections are more accurate when the affected muscles are targeted *via* needle electromyography or under ultrasound guidance. This conventional method is not supported by evidence, but correct muscle selection has been confirmed to be a key feature in the efficacy of BTX treatment[42,43].

COMBINATION OF BTX THERAPY AND NEUROREHABILITATION

As mentioned above, BTX improves motor function by reducing muscular spasticity in post-stroke patients. Therefore, BTX therapy may be a useful adjuvant therapy in combination with neurorehabilitation. In fact, several studies have reported that the combination of BTX therapy and physiotherapy improved motor recovery[26-28]. A recent study reported that BTX injection, followed by home-based functional training, may have the potential to improve active motor function of the affected upper limb in post-stroke patients[26]. Moreover, previous studies have reported that casting and dynamic splinting following BTX-A injection improved range of motion as well as motor function[5,27,28]. Thus, BTX when combined with physiotherapy or casting may be useful for improving motor function in stroke-induced spasticity.

Recently, various neurorehabilitation strategies have been established to improve neural plasticity and motor recovery. These approaches include constraint-induced

movement therapy (CIMT), transcutaneous electrical neuromuscular stimulation (TENS) and non-invasive brain stimulation (NIBS)[44-49]. A preliminary study demonstrated that the combination of BTX injection and CIMT may improve functional gains in post-stroke patients[44,45]. Moreover, a recent study reported that combined BTX-A and NIBS improves motor function in patients with stroke-induced upper limb hemiparesis[48]. However, a previous study reported that combining BTX injection with TENS did not have any additional effect on motor recovery[47]. The number of these combination studies remains small and their results are considered preliminary and controversial. Although BTX-A probably enhances the effects of neurorehabilitation strategies in post-stroke patients, future studies are required to determine the appropriate combination of treatments for optimum motor recovery.

ADVERSE EVENTS

In general, pain, rash, edema and muscle weakness have been noted at the injection site and remote muscle weakness, fatigue and allergic reaction have been reported as adverse events related to BTX therapy. To clarify the safety of BTX-A, Turkel *et al*[50] analyzed 9 double-blind, placebo-controlled studies in more than 500 patients who had experienced a stroke. The most frequent reported adverse events by the patients (> 5% but < 10% in either group) were respiratory infection, seizures, incoordination and injection site pain, none of which occurred at a significantly high rate in the BTX-A group. Nausea alone was reported at a significantly higher rate in the BTX-A group than in the placebo group. In contrast, injection site pain, chest pain and allergic reaction were found at a significantly higher frequency in the placebo group. Other reviews have also reported no serious adverse events after BTX-A administration in adult post-stroke patients[35]. Therefore, BTX has recently been considered a safe and efficacious treatment for spasticity in post-stroke patients.

However, care should be taken to try to avoid producing neutralizing antibodies. A higher dose per treatment, repetitive treatment and shorter intervals between treatments are risk factors for the production of neutralizing antibodies[51-53]. Of these, the interval between treatments is the most important risk factor. Therefore, BTX-A treatment intervals of more than three months and BTX-B treatment intervals of two months are recommended[54].

CONCLUSION

Many reports have shown the usefulness of the BTX treatment for spasticity in stroke patients. However, a few studies have reported the effectiveness of rehabilitation after BTX treatment in stroke patients. Future studies are needed to evaluate the efficacy of BTX after treatment with rehabilitation.

REFERENCES

1 **Sommerfeld DK**, Eek EU, Svensson AK, Holmqvist LW, von Arbin MH. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. *Stroke* 2004; **35**: 134-139 [PMID: 14684785 DOI: 10.1161/01.STR.0000105386.05173.5E]

2 **Lundström E**, Terént A, Borg J. Prevalence of disabling spasticity 1 year after first-ever stroke. *Eur J Neurol* 2008; **15**: 533-539 [PMID: 18355307 DOI: 10.1111/j.1468-1331.2008.02114.x]

3 **Urban PP**, Wolf T, Uebele M, Marx JJ, Vogt T, Stoeter P, Bauermann T, Weibrich C, Vucurevic GD, Schneider A, Wissel J. Occurence and clinical predictors of spasticity after ischemic stroke. *Stroke* 2010; **41**: 2016-2020 [PMID: 20705930 DOI: 10.1161/STROKEAHA.110.581991]

4 **Ward AB.** A summary of spasticity management--a treatment algorithm. *Eur J Neurol* 2002; **9** Suppl 1**:** 48-52; dicussion 53-61 [PMID: 11918650 DOI: 10.1046/j.1468-1331.2002.0090s1048.x]

5 **Farina S**, Migliorini C, Gandolfi M, Bertolasi L, Casarotto M, Manganotti P, Fiaschi A, Smania N. Combined effects of botulinum toxin and casting treatments on lower limb spasticity after stroke. *Funct Neurol* 2008; **23**: 87-91 [PMID: 18671909]

6 **Reiter F**, Danni M, Lagalla G, Ceravolo G, Provinciali L. Low-dose botulinum toxin with ankle taping for the treatment of spastic equinovarus foot after stroke. *Arch Phys Med Rehabil* 1998; **79**: 532-535 [PMID: 9596394 DOI: 10.1016/S0003-9993(98)90068-5]

7 **Verplancke D**, Snape S, Salisbury CF, Jones PW, Ward AB. A randomized controlled trial of botulinum toxin on lower limb spasticity following acute acquired severe brain injury. *Clin Rehabil* 2005; **19**: 117-125 [PMID: 15759526]

8 **Richardson D**. Physical therapy in spasticity. *Eur J Neurol* 2002; **9** Suppl 1: 17-22; dicussion 53-61 [PMID: 11918645 DOI: 10.1191/0269215505cr827oa]

9 **Intiso D**. Therapeutic use of botulinum toxin in neurorehabilitation. *J Toxicol* 2012; **2012**: 802893 [PMID: 21941544 DOI: 10.1155/2012/802893]

10 **Das Gupta BR**, Sugiyama H. Role of a protease in natural activation of Clostridium botulinum neurotoxin. *Infect Immun* 1972; **6**: 587-590 [PMID: 4564288]

11 **Pearce LB**, First ER, MacCallum RD, Gupta A. Pharmacologic characterization of botulinum toxin for basic science and medicine. *Toxicon* 1997; **35**: 1373-1412 [PMID: 9403963 DOI: 10.1016/S0041-0101(96)00180-8]

12 **Keller JE**. Recovery from botulinum neurotoxin poisoning in vivo. *Neuroscience* 2006; **139**: 629-637 [PMID: 16490322 DOI: 10.1016/j.neuroscience.2005.12.029]

13 **Comella CL**, Jankovic J, Shannon KM, Tsui J, Swenson M, Leurgans S, Fan W. Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia. *Neurology* 2005; **65**: 1423-1429 [PMID: 16275831 DOI: 10.1212/01.wnl.0000183055.81056.5c]

14 **Barnes MP**, Best D, Kidd L, Roberts B, Stark S, Weeks P, Whitaker J. The use of botulinum toxin type-B in the treatment of patients who have become unresponsive to botulinum toxin type-A -- initial experiences. *Eur J Neurol* 2005; **12**: 947-955 [PMID: 16324088 DOI: 10.1111/j.1468-1331.2005.01095.x]

15 **Factor SA**, Molho ES, Evans S, Feustel PJ. Efficacy and safety of repeated doses of botulinum toxin type B in type A resistant and responsive cervical dystonia. *Mov Disord* 2005; **20**: 1152-1160 [PMID: 15954134 DOI: 10.1002/mds.20531]

16 **Brashear A**, Gordon MF, Elovic E, Kassicieh VD, Marciniak C, Do M, Lee CH, Jenkins S, Turkel C. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002; **347**: 395-400 [PMID: 12167681 DOI: 10.1056/NEJMoa011892]

17 **Bakheit AM**, Pittock S, Moore AP, Wurker M, Otto S, Erbguth F, Coxon L. A randomized, double-blind, placebo-

controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke. *Eur J Neurol* 2001; **8**: 559-565 [PMID: 11784339 DOI: 10.1046/j.1468-1331.2001.00277.x]

18 **Simpson DM**, Alexander DN, O'Brien CF, Tagliati M, Aswad AS, Leon JM, Gibson J, Mordaunt JM, Monaghan EP. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 1996; **46**: 1306-1310 [PMID: 8628472 DOI: 10.1212/WNL.46.5.1306]

19 **Rosales RL**, Chua-Yap AS. Evidence-based systematic review on the efficacy and safety of botulinum toxin-A therapy in post-stroke spasticity. *J Neural Transm* 2008; **115**: 617-623 [PMID: 18322637 DOI: 10.1007/s00702-007-0869-3]

20 **Cardoso E**, Rodrigues B, Lucena R, Oliveira IR, Pedreira G, Melo A. Botulinum toxin type A for the treatment of the upper limb spasticity after stroke: a meta-analysis. *Arq Neuropsiquiatr* 2005; **63**: 30-33 [PMID: 15830061 DOI: 10.1590/S0004-282X2005000100006]

21 **Yablon SA,** Brin MF, VanDenburgh AM, Zhou J, Garabedian-Ruffalo SM, Abu-Shakra S, Beddingfield FC 3rd. Dose response with onabotulinumtoxinA for post-stroke spasticity: a pooled data analysis. *Mov Disord* 2011; **26**: 209-215 [PMID: 20960474 DOI: 10.1002/mds.23426]

22 **Grazko MA**, Polo KB, Jabbari B. Botulinum toxin A for spasticity, muscle spasms, and rigidity. *Neurology* 1995; **45**: 712-717 [PMID: 7723960 DOI: 10.1212/WNL.45.4.712]

23 **Burbaud P**, Wiart L, Dubos JL, Gaujard E, Debelleix X, Joseph PA, Mazaux JM, Bioulac B, Barat M, Lagueny A. A randomised, double blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients. *J Neurol Neurosurg Psychiatry* 1996; **61**: 265-269 [PMID: 8795597 DOI: 10.1136/jnnp.61.3.265]

24 **Dunne J.** Botulinum toxin type A (BOTOX) in the treatment of lower limb spasticity during stroke rehabilitation. *Intern Med J* 2003; **33** (Suppl): A41-A54

25 **Mancini F**, Sandrini C, Moglia A, Nappi G, Pacchetti C. A randomised, double-blind, dose-ranging study to evaluate efficacy and safety of three doses of botulinum toxin type A (Botox) for the treatment of spastic foot. *Neurol Sci* 2005; **26**: 26-31 [PMID: 15877184 DOI: 10.1007/s10072-005-0378-9]

26 **Takekawa T**, Kakuda W, Taguchi K, Ishikawa A, Sase Y, Abo M. Botulinum toxin type A injection, followed by home-based functional training for upper limb hemiparesis after stroke. *Int J Rehabil Res* 2012; **35**: 146-152 [PMID: 22453625 DOI: 10.1097/MRR.0b013e3283527f4a]

27 **Yaşar E**, Tok F, Safaz I, Balaban B, Yilmaz B, Alaca R. The efficacy of serial casting after botulinum toxin type A injection in improving equinovarus deformity in patients with chronic stroke. *Brain Inj* 2010; **24**: 736-739 [PMID: 20334469 DOI: 10.3109/02699051003610524]

28 **Lai JM**, Francisco GE, Willis FB. Dynamic splinting after treatment with botulinum toxin type-A: a randomized controlled pilot study. *Adv Ther* 2009; **26**: 241-248 [PMID: 19194671 DOI: 10.1007/s12325-008-0139-2]

29 **Foley N**, Pereira S, Salter K, Fernandez MM, Speechley M, Sequeira K, Miller T, Teasell R. Treatment with botulinum toxin improves upper-extremity function post stroke: a systematic review and meta-analysis. *Arch Phys Med Rehabil* 2013; **94**: 977-989 [PMID: 23262381 DOI: 10.1016/j.apmr.2012.12.006]

30 **Francisco GE**. Botulinum toxin for post-stroke spastic hypertonia: a review of its efficacy and application in clinical practice. *Ann Acad Med Singapore* 2007; **36**: 22-30 [PMID: 17285183]

31 **Foley N**, Murie-Fernandez M, Speechley M, Salter K, Sequeira K, Teasell R. Does the treatment of spastic equinovarus deformity following stroke with botulinum toxin increase gait velocity? A systematic review and meta-analysis. *Eur J Neurol* 2010; **17**: 1419-1427 [PMID: 20491885 DOI: 10.1111/j.1468-1331.2010.03084.x]

32 **Kaji R**, Osako Y, Suyama K, Maeda T, Uechi Y, Iwasaki M. Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial. *J Neurol* 2010; **257**: 1330-1337 [PMID: 20358216 DOI: 10.1007/s00415-010-5526-3]

33 **Wissel J**, Ward AB, Erztgaard P, Bensmail D, Hecht MJ, Lejeune TM, Schnider P, Altavista MC, Cavazza S, Deltombe T, Duarte E, Geurts AC, Gracies JM, Haboubi NH, Juan FJ, Kasch H, Kätterer C, Kirazli Y, Manganotti P, Parman Y, Paternostro-Sluga T, Petropoulou K, Prempeh R, Rousseaux M, Slawek J, Tieranta N. European consensus table on the use of botulinum toxin type A in adult spasticity. *J Rehabil Med* 2009; **41**: 13-25 [PMID: 19197564 DOI: 10.2340/16501977-0303]

34 **Ozcakir S**, Sivrioglu K. Botulinum toxin in poststroke spasticity. *Clin Med Res* 2007; **5**: 132-138 [PMID: 17607049 DOI: 10.3121/cmr.2007.716]

35 **Elia AE**, Filippini G, Calandrella D, Albanese A. Botulinum neurotoxins for post-stroke spasticity in adults: a systematic review. *Mov Disord* 2009; **24**: 801-812 [PMID: 19224614 DOI: 10.1002/mds.22452]

36 **Kaji R**, Osako Y, Suyama K, Maeda T, Uechi Y, Iwasaki M. Botulinum toxin type A in post-stroke upper limb spasticity. *Curr Med Res Opin* 2010; **26**: 1983-1992 [PMID: 20569068 DOI: 10.1185/03007995.2010.497103]

37 **Elovic EP**, Brashear A, Kaelin D, Liu J, Millis SR, Barron R, Turkel C. Repeated treatments with botulinum toxin type a produce sustained decreases in the limitations associated with focal upper-limb poststroke spasticity for caregivers and patients. *Arch Phys Med Rehabil* 2008; **89**: 799-806 [PMID: 18452724 DOI: 10.1016/j.apmr.2008.01.007]

38 **Pulman J**, Buckley E, Clark-Carter D. A meta-analysis evaluating the effectiveness of two different upper limb hemiparesis interventions on improving health-related quality of life following stroke. *Top Stroke Rehabil* 2013; **20**: 189-196 [PMID: 23611859 DOI: 10.1310/tsr2002-189]

39 **Francisco GE**, Boake C, Vaughn A. Botulinum toxin in upper limb spasticity after acquired brain injury: a randomized trial comparing dilution techniques. *Am J Phys Med Rehabil* 2002; **81**: 355-363 [PMID: 11964576 DOI: 10.1097/00002060-200205000-00007]

40 **Mayer NH**, Whyte J, Wannstedt G, Ellis CA. Comparative impact of 2 botulinum toxin injection techniques for elbow flexor hypertonia. *Arch Phys Med Rehabil* 2008; **89**: 982-987 [PMID: 18452749 DOI: 10.1016/j.apmr.2007.10.022]

41 **Gracies JM**, Lugassy M, Weisz DJ, Vecchio M, Flanagan S, Simpson DM. Botulinum toxin dilution and endplate targeting in spasticity: a double-blind controlled study. *Arch Phys Med Rehabil* 2009; **90**: 9-16.e2 [PMID: 19154823 DOI: 10.1016/j.apmr.2008.04.030]

42 **Cordivari C**, Misra VP, Vincent A, Catania S, Bhatia KP, Lees AJ. Secondary nonresponsiveness to botulinum toxin A in cervical dystonia: the role of electromyogram-guided injections, botulinum toxin A antibody assay, and the extensor digitorum brevis test. *Mov Disord* 2006; **21**: 1737-1741 [PMID: 16874756 DOI: 10.1002/mds.21051]

43 **Schnitzler A**, Roche N, Denormandie P, Lautridou C, Parratte B, Genet F. Manual needle placement: accuracy of botulinum toxin A injections. *Muscle Nerve* 2012; **46**: 531-534 [PMID: 22987693 DOI: 10.1002/mus.23410]

44 **Levy CE**, Giuffrida C, Richards L, Wu S, Davis S, Nadeau SE. Botulinum toxin a, evidence-based exercise therapy, and constraint-induced movement therapy for upper-limb hemiparesis attributable to stroke: a preliminary study. *Am J Phys Med Rehabil* 2007; **86**: 696-706 [PMID: 17709993 DOI: 10.1097/PHM.0b013e31813e2b4d]

45 **Sun SF**, Hsu CW, Hwang CW, Hsu PT, Wang JL, Yang CL. Application of combined botulinum toxin type A and modified constraint-induced movement therapy for an individual with chronic upper-extremity spasticity after stroke. *Phys*

Ther 2006; **86**: 1387-1397 [PMID: 17012643 DOI: 10.2522/ptj.20050262]

46 **Santamato A**, Notarnicola A, Panza F, Ranieri M, Micello MF, Manganotti P, Moretti B, Fortunato F, Filoni S, Fiore P. SBOTE study: extracorporeal shock wave therapy versus electrical stimulation after botulinum toxin type a injection for post-stroke spasticity-a prospective randomized trial. *Ultrasound Med Biol* 2013; **39**: 283-291 [PMID: 23245824 DOI: 10.1016/j.ultrasmedbio.2012.09.019]

47 **Weber DJ,** Skidmore ER, Niyonkuru C, Chang CL, Huber LM, Munin MC. Cyclic functional electrical stimulation does not enhance gains in hand grasp function when used as an adjunct to onabotulinumtoxinA and task practice therapy: a single-blind, randomized controlled pilot study. *Arch Phys Med Rehabil* 2010; **91:** 679-686 [PMID: 20434603 DOI: 10.1016/J.apmr.2010.01.010]

48 **Kakuda W**, Abo M, Momosaki R, Yokoi A, Fukuda A, Ito H, Tominaga A, Umemori T, Kameda Y. Combined therapeutic application of botulinum toxin type A, low-frequency rTMS, and intensive occupational therapy for post-stroke spastic upper limb hemiparesis. *Eur J Phys Rehabil Med* 2012; **48**: 47-55 [PMID: 22071503 DOI: 10.1097/01.phm.0000193505.85874.61]

49 **Bayram S**, Sivrioglu K, Karli N, Ozcan O. Low-dose botulinum toxin with short-term electrical stimulation in post-stroke spastic drop foot: a preliminary study. *Am J Phys Med Rehabil* 2006; **85**: 75-81 [PMID: 16357552]

50 **Turkel CC**, Bowen B, Liu J, Brin MF. Pooled analysis of the safety of botulinum toxin type A in the treatment of post-stroke spasticity. *Arch Phys Med Rehabil* 2006; **87**: 786-792 [PMID: 16731213 DOI: 10.1016/j.apmr.2006.02.015]

51 **Dressler D**. Clinical features of antibody-induced complete secondary failure of botulinum toxin therapy. *Eur Neurol* 2002; **48**: 26-29 [PMID: 12138306 DOI: 10.1159/000064953]

52 **Greene P**, Fahn S, Diamond B. Development of resistance to botulinum toxin type A in patients with torticollis. *Mov Disord* 1994; **9**: 213-217 [PMID: 8196686 DOI: 10.1002/mds.870090216]

53 **Hatheway CL,** Dang C. Immunogenicity of the neurotoxins of Clostridium botulinum. In: Jankovic J, Hallett M, eds. Therapy with Botulinum Toxin. New York: Marcel Dekker, 1994: 93-107

54 **Varghese-Kroll E**, Elovic EP. Contralateral weakness and fatigue after high-dose botulinum toxin injection for management of poststroke spasticity. *Am J Phys Med Rehabil* 2009; **88**: 495-499 [PMID: 19454855 DOI: 10.1097/PHM.0b013e3181a5b056]

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