

BOTULINUM TOXIN TYPE A FOR THE TREATMENT OF THE UPPER LIMB SPASTICITY AFTER STROKE

A meta-analysis

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ABSTRACT - Muscle over-activity is one of the cardinal features of spasticity and it is a common disability of stroke patients. In this group, spasticity is responsible for several limitations that interfere in their daily activities and quality of life. To treat spasticity, neurologists usually prescribe drugs as baclofen, tizanidine or benzodiazepines or even use definitive treatment as phenol or surgery. Authors suggest the use of botulinum toxin type A (BTX-A) for spasticity in the upper limbs after stroke, but there are few papers with adequate methodology supporting this idea. In this article we summarize the data of previous double-blind, randomized clinical trials to assess, with a meta-analysis, if BTX-A is an adequate treatment for spasticity due to stroke. The results show a statistical superiority of BTX-A over placebo on reducing muscle tone by the Modified Ashworth Scale (WMD= 0.95 [0.74 to 1.17]) in patients with post-stroke upper limb spasticity.

KEY WORDS: stroke, spasticity, botulinum toxin, rehabilitation.

Toxina botulínica tipo A para o tratamento da espasticidade de membros superiores pós-AVC: metanálise

RESUMO - Hiperatividade muscular é um dos principais sinais encontrados na espasticidade e seqüela comum após acidente vascular encefálico (AVC). Nesse grupo de pacientes, a espasticidade é responsável por limitações que interferem nas atividades diárias e qualidade de vida. Para tratar a espasticidade, neurologistas geralmente prescrevem drogas como baclofeno, tizanidina, benzodiazepínicos ou mesmo intervenções definitivas como fenol e cirurgia. Há quase duas décadas que a toxina botulínica tipo A (BTX-A) vem sendo utilizada para tratamento da espasticidade nos membros superiores pós-AVC; no entanto, há poucos artigos com metodologia adequada apoiando esta assertiva. Neste artigo avaliamos todos os dados de ensaios clínicos duplo-cegos e randomizados para definir, através de metanálise, se BTX-A é um tratamento adequado para espasticidade pós-AVC. Os nossos resultados mostram superioridade estatística da BTX-A sobre o placebo na redução do tônus muscular pela escala de Ashworth modificada (WMD= 0.95 [0.74 to 1.17]) em pacientes com espasticidade de membros superiores pós-AVC.

PALAVRAS-CHAVE: AVC, espasticidade, toxina botulínica, reabilitação.

Stroke is the most important cause of neurological disabilities in adults¹. Severe hypertonia of upper limb muscles is a common complication in these patients². About 5% of stroke patients regain useful function of the paralysed arm and the prospects of recovery after 3 months are usually negligible³. Although the muscle weakness and loss of ability are important factors in the motor functional disability in these patients, the contribution of muscle spasticity is often quite significant. Spasticity frequent-

ly causes difficulties with activities of daily living, such as dressing and cleaning the palm of the clenched hand. It may also interfere with voluntary motor function in patients with residual muscle power⁴. In some patients, severe hypertonia causes pain, discomfort and psychological disturbance with poor self-esteem and body image⁵. In these patients botulinum toxin treatment presents an opportunity to reduce disability by blocking acetylcholine release at the neuromuscular junction.

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Despite the great number of authors suggesting the use of botulinum toxin type A (BTX-A) for spasticity in the upper limbs, there are few papers with adequate methodology to support this idea.

In this article we summarize the data of previous randomised clinical trials to assess if botulinum toxin is an adequate treatment for spasticity due to stroke.

METHOD

In a systematic review of literature, we selected all double-blind, placebo-controlled, randomized clinical trials (RCT) evaluating the safety and efficacy of BTX-A for the treatment of spasticity in the upper limbs after stroke. Only data presented as, or allowing transformation into, mean±standard deviation were considered for analysis.

The searches were performed by means of Medline, Cochrane Library, Bireme, Web of Science, and Scisearch databases between 1989 (year of approval of botulinum toxin in humans by FDA) and 2004, using the words "botulinum toxin" "spasticity" and "stroke". Then, references of every selected study were checked with the purpose of identifying studies not found on electronic search. The studies were selected and the quality of the RCT evaluated by three independent reviewers using the method proposed by Jadad et al.⁶ The measured outcomes were any change in the Modified Ashworth Scale (MAS)⁷ or in the physician's and patient's Global Assessment Scale (GAS)⁸.

Data were analysed with the statistical packs Revman 4.0 from Cochrane Collaboration, and SPSS (Statistical Package for the Social Sciences), v9.0.

RESULTS

From the 98 selected papers, six fulfilled all inclusion criteria⁸⁻¹³. Despite one study⁸ presented the described criteria, it was excluded from the meta-analysis because it did not present comparable data to be analysed (Table 1).

Table 1. Characteristics of 5 double-blind, parallel group, placebo controlled studies included in the meta-analysis.

Authors	Date of first publication or report	N	Dose (units)
Simpson et al. ⁹	1996	37	BOTOX® 75/150/300
Smith et al. ¹⁰	2000	25	DYSPORT® 500/1000/1500
Bakheit et al. ¹¹	2000	82	DYSPORT® 500/1000/1500
Bakheit et al. ¹²	2001	59	DYSPORT® 1000
Brashear et al. ¹³	2002	126	BOTOX® 200 to 240

The individuals included in the studies have not been previously submitted to other pharmacological or surgical treatment for spasticity and all of them were doing physiotherapy.

All of the studies described the clinical data referring from the period between the fourth and sixth weeks after the application of the botulinum toxin and these data were used in the analysis.

Because heterogeneity ($\chi^2=2,63$; d.f.=2; $p=0,007$) was seen when clinical improvement was tested to compare the botulinum toxin group to placebo, using either MAS or GAS, by means of a fixed effect model (OR= 3.38; 95% CI= 1.34 to 8.52), a random effects model was used, confirming the results (OR= 3.31, 95% CI= 1.18 to 9.26).

Clinical improvement was also tested using the modified Ashworth Scale and this result was confirmed as well (WMD= 0.95, 95% CI= 0.74 to 1.17). Mean clinical improvement was higher in the botulinum group (Z= 8.57, $p< 0.00001$) at 4-6 week period of the study. Mean MAS score change was also higher, when wrist joint was included at the same endpoint (Z= 8.44, $p< 0.00001$).

The mean GAS scores improvement were significantly higher in all parameters of the botulinum group (WMD=1.11, 95% CI= 0.81 to 1.41, Z=7 .32, df= 1, $p<0.00001$).

Safety analysis was not possible, due to lack of adequate data in the selected studies, since only one study described side effects or adverse events, showing headache and pain as main complaints in both groups.

The results of the meta-analysis are summarized below. Related to the GAS parameters, two among three studies included in this meta-analysis did not show statistically significant difference in the botulinum toxin response. When all the studies were analysed, it was verified a better therapeutic response in the toxin group, compared to the placebo with an OR: 3.27 (IC95%: 1.38-7.74) (Fig 1).

Related to the response comparison using the Ashworth scale (Fig 2), all of the included studies showed singly a better therapeutic response in the toxin group. In the whole data it was verified WMD 0.95 (IC95%: 0.74-1.17).

DISCUSSION

Our study shows that BTX-A is superior to placebo in reducing upper limb spasticity after stroke. BTX-A in these patients is well tolerated and not associated with serious adverse events.

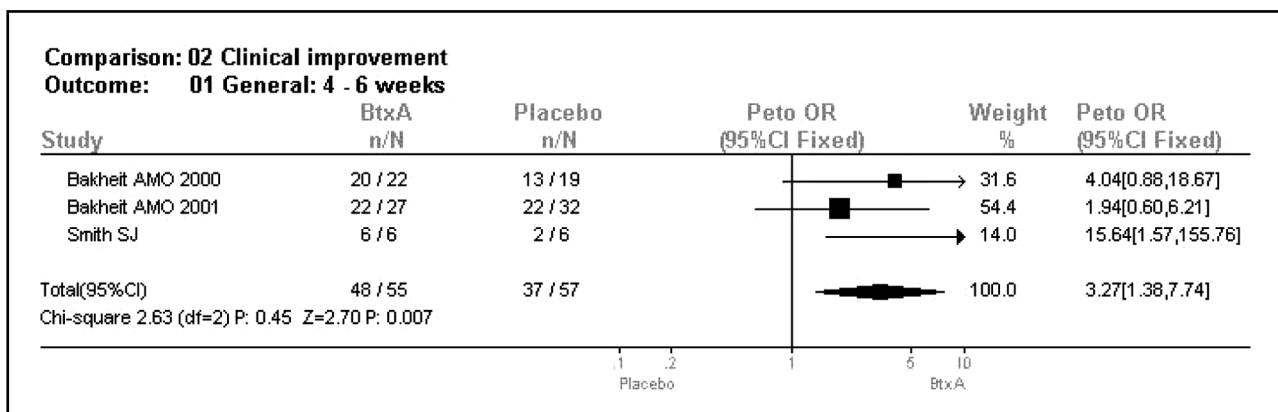


Fig 1. Comparison of GAS score in the groups using BTX and placebo.

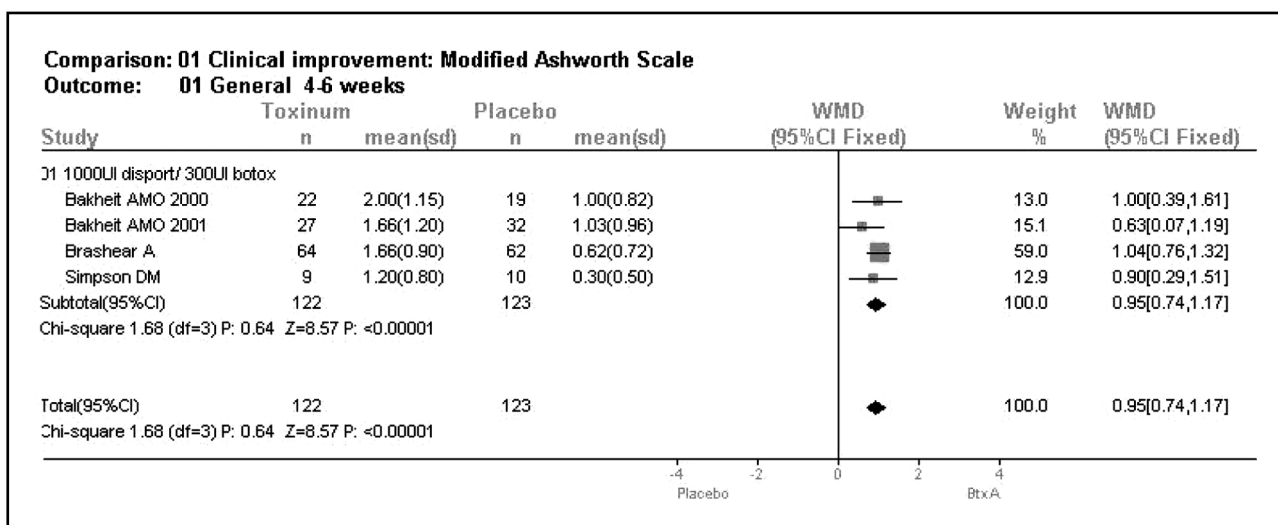


Fig 2. Change in Modified Ashworth scale from baseline at follow-up visits.

The primary efficacy measure in all but one paper was muscle tone activity using the MAS or GAS scale. Independent of doses or BTX-A used (Botox® or Dysport®) the peak reduction of muscle tone was obtained at weeks four and six after injection and returned to baseline between 10 and 16 weeks. Although the outcomes show that treatment with BTX-A in patients with upper limb spasticity resulted in statistically significant reduction in muscle tone, its overall effect in functional disability was not fully observed by the majority of authors. In all revised papers patients were enrolled in physiotherapy programs, but there was no specific occupational therapy described and few authors applied functional or quality of life measures. Furthermore, the studied population had different time of post-stroke spasticity and some patients were probably adapted to their spasticity. Another matter of concern is related to standardize muscles to apply BTX-A. As

has been stressed by Simpson et al.⁹ additional functional gains can be obtained using BTX-A in specific spastic muscles and some investigators have demonstrated that even though disability scores are unchanged, patients were capable to perform self care, which emphasises the necessity of more sensitive scales to reveal benefits associated to patients goals and subjective experience of improvement. Some scales as the Barthel Index or the Functional Independent Measures have not enough accuracy to identify modifications in quality of life secondary to reduction in muscle spasticity. The spasticity is variable from patient to patient and individualised scales will be necessary to measure specific goals¹⁴. Brashear et al.¹³ analysed functional aspects of post-stroke patients with wrist and finger spasticity submitted to intra-muscular injection of BTX-A or placebo. These authors observed significant improvement of functional disability in pa-

tients that received BTX-A when compared to placebo group, emphasising the importance of BTX-A in clinical rehabilitation. In our view, the decrease of muscle tone in upper limb spastic patients is only part of treatment. In this way, the possibility of hygiene in arm-pit and palm of the hand as well as possibility of physiologic postures to decrease habit-forming contractions have important role in the quality of life. Although spasticity is frequently associated with pain, this symptom was poorly analysed and it was not possible to be compared.

In summary this meta-analysis shows that BTX-A decreases spasticity, is a safe therapeutic agent and also suggests that it probably improves quality of life in upper limb spastic patients. There is no information about long-term use of BTX-A.

REFERENCES

1. Nakaiama H, Jorgensen HS, Raaschou HO, et al. Recovery of upper extremity function in stroke patients: the Copenhagen stroke study. *Arch Phys Med Rehab* 1994;75:394-398.
2. Rousseaux M, Kozlowski O, Froger J. Efficacy of botulinum toxin A in upper limb function of hemiplegic patients. *J Neurol* 2002;249:76-84
3. Wade DT. Physiotherapy intervention late after stroke and morbidity. *BMJ* 1992;304:609-613.
4. Mizrahi EM, Angel RW. Impairment of voluntary movement by spasticity. *Ann Neurol*. 1979;5:494-495.
5. Blasi J, Chapman ER, Link E, et al. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. *Nature* 1993;365:160-163.
6. Jadad AR, Moore A, Carrol D. Assessing the quality of reports of randomised clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
7. Bohannon RW, Smith MB. Inter-rater reliability of a modified Ashworth Scale of muscle spasticity. *Phys Ther*. 1987;67:206-207.
8. Bhakta BB, Cozens JA, Chamberlian MA, Bamford JM. Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial. *J Neurol Neurosurg Psychiatry* 2001;70:821.
9. Simpson DM, Alexander DN, O'Brien CF, et al. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomised, double-blind, placebo-controlled trial. *Neurology* 1996;46:1306-1310.
10. Smith SJ, Ellis E, White S, Moore AP. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. *Clin Rehabil* 2000;14:5-13.
11. Bakheit AM, Thilmann AF, Ward AB, et al. A randomised, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A with placebo in upper limb spasticity after stroke. *Stroke* 2000;31:2402-2406.
12. Bakheit AMO; Pittock S, Moore AP, et al. A randomised, 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.
13. Brashear A, Gordon MF, Elovic E, et al. Intra-muscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002;347:395-400.
14. Bakheit AMO. Optimising the methods of evaluation of the effectiveness of botulinum toxin treatment of post-stroke muscle spasticity. *J Neurol Neurosurg Psychiatry* 2004;75:665-666.