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Dear Editor

Please find enclosed the edited manuscript in Word format.

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

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Revisions have been made according to the reviewer suggestions.

1) Comments about the different formulations of botulinum toxin and their role in the treatment of spasticity in stroke should be made

Thank you for your suggestion. We have added the following sentences in the introduction:

Seven types of Botulinum toxin 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]. (Page 3, lines 13-17)

2) Talking about the injection method, comments about recommended doses of botulinum toxin per session, per muscle...as well as comments about muscles usually injected should be made

According to your suggestion, we have added the following sentences:

In the upper limb:

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 [30,31].(Page4, lines15-16 and page5, lines1-3)

In the lower limb and each sessions:

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, 50-150 units for the tibialis posterior [30,31]. 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) [33-35] .(Page5, lines12-18 and page6, line1)

3) I do not understand very well the sentence “...these findings suggest that a low-dose, high-volume strategy should be considered when treating patients with several involved muscles so that the dose will be within the limit specified in the total body dose guidelines...”, although this field is not solved by the evidence, current recommendations suggest to inject lower volumes and fewer points close to the neuromuscular junction in those muscle where the neuromuscular junctions are known and to inject higher volumes and more points in those muscles where the neuromuscular junctions are not known .

We agreed with your suggestion that the appropriate injection methods according to the BTX-A volume and injection points must be elucidate. We have deleted the inappropriate statement and revised the these sentences. Please see the revised paper.(Page 7, lines 4-6)

4) Although electromyography and ultrasound could be helpful in targeting the selected muscles the sentence “...BTX-A injections are more efficacious if the affected muscles are targeted via needle electromyography or under ultrasound guidance...” is not supported by the evidence.

Thank you for your suggestion. We have revised the following sentence:

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]. (Page 7, lines 6-9)

5) Comments about the development of neutralizing antibodies in the treatment of spasticity in stroke with botulinum toxin should be made

According to your suggestion, we have added the following sentences:

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].(Page 9, lines 14-18 and page 10, line 1)

6) A section of “Conclusions” should be written

According to your suggestion, we have added the following conclusion section:

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.(Page 10, lines 2-6)

We thank the reviewers and editor for their comments and inputs that have enabled us to considerably improve our paper. We hope that all the concerns raised by the reviewers and editors have been adequately addressed and that our paper is now acceptable for publication in *World Journal of Neurology*.

Sincerely yours,

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