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Safety of ultrasound-guided botulinum toxin type A injections for patients with anticoagulant and antiplatelet background medication

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Abstract

Background. TXB-A injections are the first-line treatment of many movement disorders, and the safety of doing them is essential to the effectiveness of therapy.

Aims. Evaluation of safety of TXB-A guided injections in upper limb spasticity of post-stroke patients.

Methods. The study group comprised 60 patients distributed in 3 subgroups of 20 based on background medication administered in post-stroke management: 20 patients in the antiplatelet background subgroup, 20 patients in the subgroup of anticoagulant background medication, and 20 without anticoagulant/antiplatelet background medication. From the 60 patient group, based on the number of TXB-A injection cycles, 3 other subgroups were produced: 20 patients performed 3 injection cycles, 20 performed 2 cycles, and 20 completed a single injection cycle.

Every patient received a total dose of 1000 UI of TXB-A. After each set of local injections, ultrasounds were performed at the injection site searching for local hematomas. The moments evaluated were: T0 (the initial time – injection time), T1 (one month after the injection), T2 (3 months from T0 or 2 months from T1), T3 (1 month after T2), T4 (3 months after T2 or 2 months after T3) and T5 (1 month after T4).

Results. The lowest p value of the 3 possible comparisons of the anticoagulant, antiplatelet, no anticoagulant/antiplatelet group of patients was 0.856, showing a purely random distribution of adverse effects manifested by local hematomas following ultrasound guided injections.

Conclusions. Multiple cycles of US guided TXB-A injections with a minimum 3-month frequency between injections do not increase the risk of local haematomas.

Key words: botulinum toxin type A, ultrasound guided injections, safe treatment.

Introduction

The US guided TXB-A effectiveness in the treatment of upper limb spasticity after a stroke is well established (Grigoriu et al., 2015; Popescu et al., 2018). Several guidelines and many experienced practitioners recommend TXB-A injections as a first-line treatment option, not only in spasticity, but in many other movement disorders (1); (Thibaut et al., 2018).

Although the largest use of TXB-A is still in the treatment of neurological disorders manifested by abnormal, excessive or inadequate muscle contractions, the use of TXB-A continues to extend and includes the treatment of a variety of ophthalmic, gastrointestinal, urologic, orthopedic, dermatological, dental diseases and the treatment of pain-related syndromes (Dutta et al., 2016).

Its growing use in many pathologies makes it one of the most versatile medicines of our time, covering almost all the specialties of medicine. Although it is considered effective and safe, there are still many limitations, such as injection-related discomfort, a relatively short period of action and high cost (Simpson et al., 2016).

The adverse effects of treatment with TXB-A are minor and important systemic side effects are very rare. In most cases, local pain at the injection site and local muscle weakness of nearby muscles from toxin spread are the most reported (Marciniak et al., 2019; Gracies et al., 2015).

To prevent antibody formation and implicitly failure of therapy, it is recommended to inject the lowest effective dose, to prevent short injection intervals and to alternatively use different TXB-A serotypes (Truong et al., 2013).

A variety of techniques and guidance methods can

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be used to identify the target spastic muscles. Palpation and anatomical landmarks, electromyography (EMG), electrical stimulation (ES) and ultrasound (US) are most commonly used by clinicians for guiding TXB-A injections (Tok et al., 2011).

US is a well-established, reliable guidance method that offers real-time, high-resolution images, and provides a detailed picture of a muscle: location, depth, target trajectory, other structures (nerves, vessels, organs) in the region of interest. It is less expensive, more accessible and convenient than other image-based guidance methods such as MRI, CT or fluoroscopy. A US machine with a 7.5 MHz linear transducer can ensure a quality resolution for both superficial and deep muscles (Willenborg et al., 2002).

Hypothesis

TXB-A is a first-line treatment option for focal spasticity after a stroke, and the accuracy in the transmission of the substance to the target muscles can influence the outcomes. The purpose of this study is to quantify the local adverse effects at the injection site after TXB-A guided injections and to establish if US is a reliable and safe guidance method.

Objectives

a) Correlations between higher and lower doses of TXB-A administered to a muscle and the appearance of local adverse effects

b) Correlations between patient background medication in stroke management: antiplatelet/anticoagulant and appearance of adverse effects following TXB-A guided injections

c) Assessing the safety of US in guiding local injections with TXB-A

Material and methods

Research protocol

a) Period and place of the research

The observational study was performed in the Rehabilitation Department of the Elias University Hospital in the period September 2017 - March 2018. The study was approved by the Ethics Committee of the Elias University Hospital (08.08.2017), according to the Good Practice Guidelines. All 60 patients who participated in the study gave their consent to the use and publication of the results for research purposes.

b) Subjects and groups

The study group was formed by 60 patients with upper limb spasticity, who were divided into 2 subgroups (250 IU versus 333 IU), based on the doses injected in the wrist and finger flexors. Patients receiving 250 IU were injected in 4 muscles, while those receiving 333 UI were injected in 3 muscles.

The 60 patients of the group were distributed in another 3 subgroups of 20 based on the background medication administered in post-stroke management: 20 patients in the antiplatelet background subgroup, 20 patients in the subgroup of anticoagulant background medication, and 20 patients without anticoagulant/antiplatelet background medication. Of the 60 patient group, based on the number of TXB-A injection cycles, 3 other subgroups were formed: 20 patients performed 3 injection cycles, 20 performed 2 cycles, and 20 completed a single injection cycle. Each patient received a total dose of 1000 IU of TXB-A.

c) Tests applied

After each set of local injections, ultrasound was performed at the injection site searching for local hematoma. The moments evaluated were: T0 (the initial time - injection time), T1 (one month after the injection), T2 (3 months after T0 or 2 months after T1), T3 (1 month after T2), T4 (3 months after T2 or 2 months after T3) and T5 (1 month after T4).

d) Statistical processing

The Mann-Whitney *U* test was used to statistically process the results.

The objective was to check whether the injection cycles had a contribution in the appearance of hematomas, measured in the 3 groups created based on the background medication. A comparison was made based on the number of injected muscles. We recall that according to the injection sessions, patients were grouped into three categories: one cycle, two or three cycles. Patients were divided depending on the number of injected muscles, on the dose administered into a muscle, respectively: the 1000 IU were distributed in 3 or 4 muscles, i.e. 333 IU/muscle or 250 IU/muscle.

For example, a patient with 3 injection cycles and 4 injected muscles was actually injected 12 times. One with one injection cycle and 3 injected muscles was injected 3 times. These are actually the top and bottom limits of our data on cumulative injections, so we will compare the independent groups between them based on the background medication categories. The data is considered scale type because 0 has a meaning (no hematoma encountered).

Results

The objective of the study was to show that local injections of TXB-A under ultrasound guidance are safe regardless of the anticoagulant or antiplatelet medication used by the patient in the background treatment. Thus, we gathered the number of local injections performed in each of the 3 patient groups and analyzed the appearance of hematomas within a group of patients and between the 3 groups formed.

It can be seen that there is no statistical difference between those who did not receive additional background medication, those who received anticoagulants and those who received antiplatelets. This shows that regardless of the number of injections received, adverse effects are not influenced. Regarding the cumulative number of injected muscles, 120, 156 or 144, the total number of hematomas was 9, which were randomly distributed, 4 in the anticoagulant group, 3 in the antiplatelet group, 2 in the group of patients with no background medication.

The results are presented in Tables I to III.

Discussions

This study shows that neither the dose injected in a muscle nor the number of injection sessions or injected muscles affects the appearance of hematoma, regardless of the type of background medication used. This contributes to

Table I

Statistical comparison of the number of hematomas after local injection: no background medication group/antiplatelet group.

Patient groups	No. of hematomas	No. of muscles injected	No. of patients	Average	Median	Standard deviation	Comparative test	p-value
No background medication	2	120	18	0.11	0	0.323	Mann-Whitney U	0.878
Antiplatelet	3	156	21	0.14	0	0.359		

Table II

Statistical comparison of the number of hematomas after local injection: no background medication group/anticoagulant group.

Patient groups	No. of hematomas	No. of muscles injected	No. of patients	Average	Median	Standard deviation	Comparative test	p-value
No background medication	2	120	18	0.11	0	0.323	Mann-Whitney U	0.856
Anticoagulant	4	144	21	0.19	0	0.512		

Table III

Statistical comparison of the number of hematomas after local injection: antiplatelet group/anticoagulant group.

Patient groups	No. of hematomas	No. of muscles injected	No. of patients	Average	Median	Standard deviation	Comparative test	p-value
Antiplatelet	3	156	21	0.14	0	0.359	Mann-Whitney U	0.950
Anticoagulant	4	144	21	0.19	0	0.512		

the safety with which injections can be delivered under US guidance: the lowest p-value of the 3 comparisons/possible combinations was 0.856, meaning that the distribution of hematomas was purely random.

In many recent studies, it has been shown that the use of US guidance for local injections of TXB-A increases efficiency and accuracy (Jabbari, 2016). It is well established that US guidance along with electrical stimulation guidance offers the most effective local technique of injection (Walker et al., 2015), but although US does not provide information on muscle activity, it provides information about muscle size and the degree of local fibrosis, very important aspects in making the decision to inject, ensuring increased safety for the intervention (Malloy et al., 2002).

Taking into account that TXB-A is not a curative treatment of spasticity, and the effect generally lasts between 2 and 4 months, patients with spasticity requiring the repeat of the injections after this period, we consider this study to be very important because it shows that multiple sessions with a minimum period of 3 months between them do not cause local adverse effects.

In addition, in a recent study (Trompetto et al., 2017), the authors showed that the low immunogenicity of current TXB-A products allows more frequent injection intervals than every 3 months, toxin-directed antibody formation is not related to the dosage and frequency of *injections*, and the most frequent adverse effects after TXB-A treatment are local, at the site of injection.

The role of US in administering TXB-A should be emphasized because, especially in the case of the upper limb, we encounter a multitude of anatomical variations of the muscles such as the inconstant presence of the palmaris longus muscle, the Gantzer variation of the flexor pollicis longus muscle, vascular-nerve variations such as Martin-Gruber anastomosis, all of which are disturbing factors in local TXB-A administration, and may cause injection errors resulting in local adverse effects (Olewnik et al., 2017).

Conclusions

1. Multiple cycles of US guided TXB-A injections with a minimum 3-month interval between injections do not increase the risk of local hematoma.

2. The presence of antiplatelet, anticoagulant background medication does not increase the risk of local adverse effects after TXB-A injections under ultrasound guidance.

3. The present study suggests that local TXB-A injections under ultrasound guidance in patients with upper limb spasticity after stroke are safe in the doses used in this study.

Conflicts of interest

Nothing to declare.

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