DO SKELETAL MUSCLE PROPERTIES RECOVER FOLLOWING REPEAT BOTULINUM TOXIN TYPE-A INJECTIONS?

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INTRODUCTION

Botulinum toxin type-A (BTX-A) is a frequently used treatment modality for a variety of neuromuscular disorders with the primary aim to relax spastic muscles. When injected into spastic muscles, it prevents the release of acetylcholine at the motor nerve endings, thus inducing a dose-dependent muscle paralysis [1].

Although considered safe, previous studies have suggested that BTX-A injections cause muscle atrophy and contractile material loss in injected and contralateral non-injected muscles [2,3]. BTX-A treatments often comprise repeat injections separated by 3-4 month intervals due to the reversible and time limited action of the toxin [4]. Depending on the BTX-A injection/recovery protocol, muscle function may be compromised following repeat BTX-A treatments and this could severely impair muscle function once BTX-A treatment has been finished. However, muscle recovery following BTX-A treatments, and its long term effects, are anecdotal with no systematic research backing the clinical claims.

Therefore, the purpose of this study was to investigate if muscle properties can fully recover within six months following monthly BTX-A injections given over a half year period.

METHODS

Twenty-seven skeletally mature one year old female NZW rabbits were divided into 5 groups as follow: Control (n=5), BTX-A+0M (n=5), BTX-A+1M (n=5), BTX-A+3M (n=5), BTX-A+6M (n=7). Control group rabbits received equal volume saline injections as experimental rabbits. Experimental rabbits received intramuscular monthly BTX-A injections (3.5U/kg) unilaterally into the quadriceps femoris musculature for six months, and were evaluated after 0, 1, 3, and 6 months of recovery (BTX-A+0M/+1M/+3M/+6M; respectively).

Outcome measures included isometric knee extensor strength, muscle mass, and contractile material percentage in quadriceps femoris injected and contralateral non-injected muscles. Muscle mass and strength were assessed by weighing the muscles and measuring the maximal isometric strength via femoral nerve stimulation throughout the entire knee range of motion. The contractile material percentage was determined histologically by the area fraction of contractile material to total muscle cross-sectional area.

A two way mixed model ANOVA with the main factors leg (injected and contralateral non-injected) and groups (Control, BTX-A+0M/+1M/+3M/+6M) was performed (α=0.05).

RESULTS

Isometric knee extensor strength was partially and completely recovered in the injected and contralateral non-injected hindlimbs, respectively for BTX-A+6M group rabbits. Peak knee extensor strength in the BTX-A injected hindlimbs was reached after 1 month of recovery (BTX-A+1M), with no further recover for BTX-A+3M and BTX-A+6M group rabbits (Fig 1). Muscle mass recovered in a similar manner to strength (results not shown).

The contractile material for Control group rabbits was around 96%. BTX-A+0M group rabbits had a significant reduction in the contractile material for the injected (63%) and contralateral non-injected (79%) hindlimbs. The contractile material was partially recovered in the injected hindlimbs for the BTX-A+6M but not for the BTX-A+1M and BTX-A+3M group rabbits when compared to BTX-A+0M group rabbits. The contractile material in the contralateral non-injected hindlimbs showed no
recovery in the BTX-A+1M/3M/6M compared to the BTX-A+0M rabbits (Fig 2).

**Figure 1** Mean (±1SE) knee extensor strength normalized to control group rabbits (dark bars). *compared to Control; #compared to BTX-A+0M group (p<0.05).

**Figure 2** Mean (±1SE) contractile material normalized to control group rabbits (dark bars). *compared to control; #compared to BTX-A+0M group (p<0.05).

**DISCUSSION AND CONCLUSIONS**

Isometric knee extensor strength, muscle mass and the area fraction of contractile material was not fully recovered in injected and contralateral non-injected quadriceps femoris muscles after six months of recovery. While knee extensor strength and muscle mass recovered to a certain degree, there was no apparent improvement in the area fraction of contractile material, suggesting that muscle mass and strength recovery occur at a different rate than the recovery of the contractile material. Since contractile material is typically not evaluated in patients suffering from spasticity following repeat BTX-A treatments, measurements of muscle strength, volume and mass may not appropriately reflect the long-term structural changes in skeletal muscles following repeat BTX-A treatments.

The dramatic recovery of strength in the BTX-A injected muscles of the 1 month recovery group compared to the 0 month recovery group suggests that the effects of BTX-A on acetylcholine release inhibition wore off primarily between the 0 and 1 month recovery period. Considering that the injections were given at the beginning of each month, the 0 month recovery rabbits were 1 month post the last injection, while the 1 month recovery rabbits were 2 months post injection. Our results, therefore, are consistent with previous findings that BTX-A effects rapidly decrease after approximately four weeks following the last BTX-A injection [5]. They also suggest that BTX-A affected not only the target muscles, but also the quadriceps muscles of the contralateral hindlimbs that were not injected and were not targeted in this investigation. Future studies will need to address the fact that long-term recovery following BTX-A treatment may affects no-target muscles and may lead to non-reversible damage of the injected musculature.

**REFERENCES**


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