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

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SUMMARY

Botulinum toxin type-A (BTX-A) is frequently used in a variety of neuromuscular disorders to relax spastic muscles by preventing acetylcholine release at the nerve endings. BTX-A injections reduce muscle tone, allowing muscles to stretch, thus increasing functionality in patients. Repeat BTX-A injections are given approximately every 3 months to prolong its diminishing effects. Optimal timing between injections is based on clinical evaluation, with little assessment of muscle structure. The purpose of this study was to investigate if muscle properties fully recover following monthly BTX-A injections. Twenty-seven NZW rabbits were divided into five groups: Control, BTX-A+0M, BTX-A+1M, BTX-A+3M, and BTX-A+6M. Control group animals received saline injections, while experimental group animals received monthly BTX-A injections (3.5U/kg) into the quadriceps muscles for six months, and were evaluated after 0, 1, 3, and 6 months of recovery. Outcome measures included strength, mass, and contractile material in the injected and contralateral non-injected quadriceps musculature. Strength and mass were partially and completely recovered in the injected and contralateral non-injected musculature, respectively. Contractile material was 96% for Control group animals. BTX-A+0M showed a reduction in contractile material for the injected (63%) and contralateral non-injected musculature (79%). Contractile material was partially recovered in the injected (77%), but did not recover in the contralateral non-injected musculature of BTX-A+6M group animals (~81%). We conclude from these results that neither injected nor contralateral non-injected muscles completely recover from a repeat BTX-A injection protocol.

INTRODUCTION

Botulinum toxin type-a (BTX-A) is a frequently used treatment modality for an increasing number of neuromuscular disorders with the primary aim to relax spastic muscles. These muscles typically have an abnormal muscle tone and overactive stretch reflex responses, resulting in muscle contractures and bony deformities. When injected into spastic muscles, BTX-A prevents acetylcholine release at the nerve endings, thus inducing a dose-dependent muscle paralysis. BTX-A injections produce a reduced muscle tone, allowing for muscles to be stretched more easily, thus increasing the joint range of motion and increasing function and independence of patients [1].

Although considered safe, BTX-A injections cause muscle atrophy, contractile material loss, and muscle weakness in injected and non-target muscles [2]. Repeat BTX-A injections are often performed with about 3 months interval between injections in order to prolong the period of reduced spasticity [3]. However, depending on the BTX-A injection/recovery period, muscle function may be compromised and could affect a patient's quality of life once treatment has been finished. Currently, BTX-A treatment protocols, and timing between repeat injections, are based on clinical and functional examination, typically not involving evaluation of muscle structure and integrity.

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

METHODS

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

The outcome measures included isometric knee extensor strength, muscle mass, and contractile material percentage in the injected quadriceps and the contralateral non-injected musculature. 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 percentage of contractile material was determined histologically by the fraction of area containing contractile material to the total muscle cross-sectional area. A two way 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 AND DISCUSSION

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

The contractile material for Control group animals was around 96%. BTX-A+0M group animals had a significant reduction in contractile material for the injected (63%) and the contralateral non-injected (79%) muscles. The contractile material was partially recovered in the injected musculature for the BTX-A+6M (77%), but not for the BTX-A+1M (70%) and BTX-A+3M (67%) group animals. The contractile material in the contralateral non-injected musculature did not recover in the BTX-A+1M/3M/6M group animals (82%, 79%, and 84%; respectively) compared to the BTX-A+0M group animals. The contractile material for the injected and contralateral non-injected experimental group animals remained smaller than Control group values at all times of recovery (Figure 2).

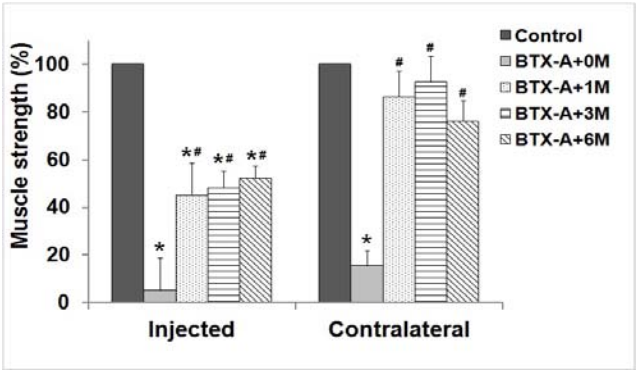

Figure 1 Mean (±1SE) knee extensor strength normalized to control group (dark bars).*****compared to Control; #compared to BTX-A+0M group ($p<0.05$).

Isometric knee extensor strength, muscle mass and percentage of contractile material were not fully recovered in the BTX-A injected musculature. While knee extensor strength and muscle mass showed a quick recovery at 1 month into recovery, the contractile material recovery was only significant at the end of the 6 months recovery period, suggesting that knee extensor strength/muscle mass recovery occur at a different rate than the contractile material recovery. Knee extensor strength and muscle mass were fully recovered for the contralateral non-injected muscles, while there was no recovery in the contractile material, suggesting that BTX-A injections may lead to long-lasting adverse effects.

In practice, spastic muscles are treated with repeat BTX-A injections based on physicians' experience and functional examination, with little attention to muscle integrity and structure. Therefore future research may not only focus on a patient's functional outcomes, but also on systematic evaluation of muscle structure and integrity at different time points during BTX-A treatment and recovery period.

CONCLUSIONS

We conclude from the results of this study that BTX-A injected and non-injected contralateral muscles in the rabbit hind limb do not recover structure, function and strength within six months following an intense BTX-A injection protocol.

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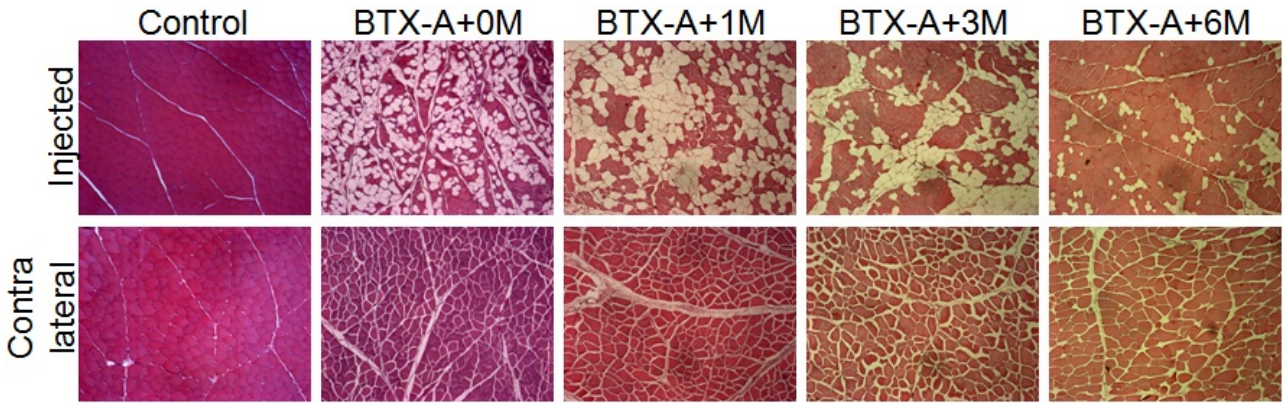

Figure 2 Histological cross-sectional images of contractile material for injected (upper row) and contralateral non-injected quadriceps musculature (lower row) for Control (first column), BTX-A+0M/1M/3M/6M group rabbits (second, third, fourth, and fifth column), respectively. Contractile material for Control group was 96%. There was a reduction of contractile material for BTX-A+0M group in the injected (first row; second column; 63%) and contralateral non-injected quadriceps (second row; second column; 79%) ($p<0.001$). The contractile material on the injected musculature only showed significant recovery ($p<0.05$) for BTX-A+6M compared to BTX-A+0M group (first row; fifth column; 77%), but did not reach Control group values ($p>0.05$). There was no significant recovery in contractile for the contralateral non-injected quadriceps musculature of BTX-A+1M/3M/6M (second row; third (82%), fourth (79%), and fifth (84%) column, respectively) compared to BTX-A+0M group ($p>0.05$), and remained smaller compared to Control group values.