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BASIC SCIENCE

The effect of muscle paralysis using Botox on the healing of tendon to bone in a rat model

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Hypothesis: Despite good clinical results after rotator cuff repair, follow-up studies show significant rates of failed healing. This may be because of excessive tension on the repaired tendon due to shoulder motion. We hypothesized that botulinum toxin A injections would result in improved attachment strength and collagen organization at the tendon-bone interface at early time points but may result in decreased mechanical properties at later time points because of the negative effects of stress deprivation.

Materials and methods: We performed division and repair of the supraspinatus tendon in 132 rats: 66 underwent repair alone and 66 received injections of botulinum toxin into the muscle before repair. Rats were killed at 4, 8, and 24 weeks and were evaluated by use of histologic, biomechanical, and micro−computed tomography analyses.

Results: At 4 and 24 weeks, there was no significant difference in load to failure between groups. At 8 weeks, the botulinum group had a significantly lower load to failure compared with controls (27.7 N vs 46.7 N, $P < .01$). The weight of the supraspinatus muscle was significantly decreased at 4 and 8 weeks in the botulinum group, but it recovered by 24 weeks. Micro−computed tomography analysis showed the botulinum group to have significantly less bone volume, total mineral content, and total mineral density at 8 weeks. Histologic analysis showed formation of a more normal tidemark and increased collagen fiber organization in the botulinum specimens at 4 weeks.

Discussion: Botulinum toxin A−treated specimens had increased collagen fiber organization at 4 weeks and decreased mechanical properties at later time points. The rapid healing of the rat rotator cuff likely makes it difficult to realize benefits from reduction in strain.

Level of evidence: Basic Science Study.

Keywords: Stress deprivation; tendon-to-bone healing; rotator cuff repair

Mini-open and arthroscopic rotator cuff repairs both show good clinical results; however, relatively high rates of retear or failed healing have been reported by use of magnetic resonance imaging and ultrasound.[3,10,11,13] In a recent study, 31% of mini-open rotator cuff repairs and 47% of arthroscopic tears failed to heal or had retorn at follow-up, with patients with failed rotator cuff repairs showing decreased strength of forward elevation and external rotation.[3] Clinical results may be improved if a lower failure rate of tendon-to-bone healing in rotator cuff repairs can be achieved.

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One potential method to decrease the high failure rate would be to temporarily paralyze the rotator cuff muscle to minimize tension on the repaired tendon for the duration of the tendon-to-bone healing process. Paralysis would prevent the muscle from firing and thus potentially avoid tension overload on the repair. Inability to activate the muscle could also allow patients to begin early active motion using other rotator cuff, deltoid, and periscapular muscles, decreasing the likelihood of postoperative stiffness and disuse atrophy, allowing patients to continue activities of daily living.

Temporary paralysis can be achieved with the use of botulinum toxin A (Allergan, Irvine, CA). Botulinum toxin A is 1 of 7 neurotoxin subtypes produced by the bacteria *Clostridium botulinum*. Botulinum toxin acts by binding presynaptically to high-affinity recognition sites on the cholinergic nerve terminals, thereby decreasing the release of acetylcholine and causing neuromuscular blockade. Recovery occurs through proximal axonal sprouting and muscle reinnervation by formation of new neuromuscular junctions. The neuronal activity begins to return at 12 weeks with new neuronal sprouting. Complete return of function occurs by 6 months.[4] Botulinum toxin A is considered safe and effective for the treatment of movement disorders and spasticity, and it has been widely used in both pediatric and adult orthopaedics for spasticity in cerebral palsy,[1,5,6,9,19,22,27] in idiopathic clubfoot,[2,26] in the pectoralis major muscle in irreducible shoulder dislocations,[29] in tennis elbow,[16,20,35] and in flexor tendon repairs in children.[33] Tuzuner et al[33] used botulinum toxin A during surgery to induce forearm flexor relaxation in children aged under 6 years with zone 2 flexor tendon repairs. They concluded that this generated a significant reduction in spontaneous activity of the fingers, which permitted an improved rehabilitation program. Ma et al[25] used botulinum toxin A in conjunction with Achilles tendon repairs in a rat model to reduce the rate of spontaneous rupture, and they showed that the rupture rate was 3 times lower than controls by 1 week. In addition, the tendon rupture force was significantly higher between 1 and 3 weeks after repair. There was no significant difference after 3 weeks. Botulinum A is currently Food and Drug Administration approved for the treatment of strabismus, blepharospasm, hemifacial spasm, cervical dystonia, and hyperhidrosis.

We used a rat rotator cuff repair model to test 2 hypotheses: (1) Botulinum toxin A would result in improved attachment strength at the healing tendon-to-bone junction. (2) The change in the loading environment would lead to improved collagen fiber organization at the healing tendon-bone interface in a rat rotator cuff repair model.

Materials and methods

Study design

We used a rat model based on work by Soslowsky et al[30] that showed anatomic similarities with the human shoulder. After we obtained approval from the Institutional Animal Care and Use Committee of the Hospital for Special Surgery (No. 07-06-06R), 132 male Sprague-Dawley rats were obtained with a mean preoperative weight of 421 g. There was no difference in weight at the time of operation between the groups. Each animal underwent detachment and immediate repair of the right supraspinatus tendon by use of bone tunnel suture fixation. The botulinum toxin A group was injected with 6 U/kg of botulinum toxin A (Allergan) through a Teflon-coated 24-gauge needle connected to a nerve stimulator before tendon detachment and repair. Figure 1 is an intraoperative photograph of the Teflon-coated needle within the supraspinatus muscle. Postoperatively, the rats were housed in pairs and allowed ad libitum activity. The animals were killed at 4, 8, and 24 weeks, and the tissues were analyzed by histology, biomechanics, and micro−computed tomography (CT).

Surgical technique

The rats were anesthetized with 100 mg/mL of ketamine and 20 mg/mL of xylazine administered intraperitoneally into the right lower abdominal quadrant. In 7 rats anesthesia was prolonged by administration of 2% isoflurane via nose cone. All operations were performed by sterile technique with the rat in the lateral position. A deltoid-splitting incision was made and the acromioclavicular joint divided to visualize the rotator cuff. The supraspinatus tendon was identified. In the botulinum toxin A group, a Teflon-coated needle attached to a nerve stimulator was inserted into the supraspinatus muscle and the location that produced maximal muscle contraction was identified. We then injected 6 U/kg of botulinum toxin A into the muscle belly, causing cessation of the contractions. The tendon was then sharply dissected off the greater tuberosity. The tuberosity was debrided of all soft tissue, and a No. 3-0 Ethibond suture (Ethicon, Somerville, NJ) was passed through the supraspinatus tendon via a Mason-Allen suture. Bone tunnels were made 2 mm from the articular surface on the greater tuberosity. The suture ends were passed through the bone tunnels and tied over the humeral cortex, reapproximating the supraspinatus to its footprint on the greater tuberosity. The deltoid split was reapproximated with No. 3-0 Ethibond, and the skin was closed with No. 3-0 Vicryl subcutaneous suture (Ethicon). Skin glue (Nexaband; Abbott Laboratories, North Chicago, IL) was applied to further protect the wound. Buprenorphine, 0.05 mg/kg, was administered subcutaneously for postoperative pain control.

Experimental groups

The rats were assigned to either the botulinum toxin A or control group preoperatively (66 animals per group). The botulinum toxin A dose (6 U/kg) was chosen based on previous studies.[24,27,28] Sacrifice times of 4, 8, and 24 weeks were used for both groups. These time points were chosen because by 8 weeks, tendon-to-bone healing is largely complete in rats, and 4 weeks is approximately midway through the healing process. It is known that complete recovery of muscle function occurs by 24 weeks after botulinum toxin A injection in the rat.[28] Three animals from each time point in each group (botulinum toxin A and control) were allocated for histologic analysis and the remaining 19 specimens at each time point allocated for biomechanical testing. A power analysis determined that 18 rats at 4 weeks, 21 rats at 8 weeks, and

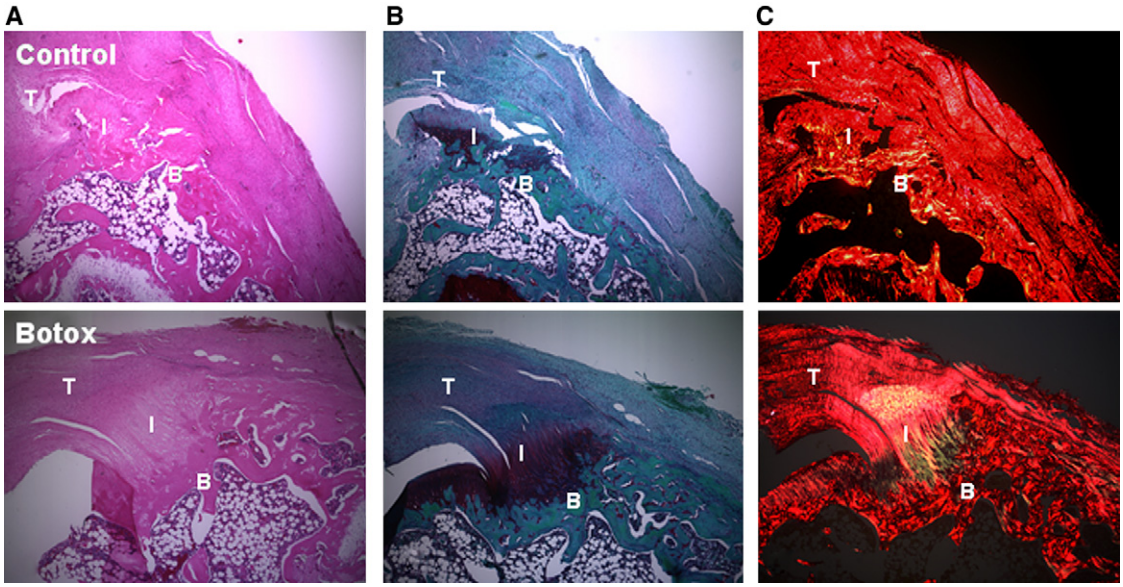

Figure 1 Hematoxylin-eosin (**A**), safranin O (**B**), and picrosirius red (**C**) images of control and botulinum toxin A specimens at 4 weeks, with botulinum specimens having increased fibrocartilage, better organized tissue, decreased cellularity, and decreased vascularity as compared with control specimens. T, supraspinatus tendon; I, interface; B, bone.

35 rats at 24 weeks would allow detection of a 20% difference with α of .05 and β of .80.

Gross inspection

Each specimen was examined visually to assess for tendon detachment and any gross differences between groups.

Histology

A total of 18 specimens underwent histologic analysis, 3 from each time point in both groups. The specimens were fixed in 10% neutral-buffered formalin for 48 hours. After fixation, tissues were decalcified in Immunocal (Decal Chemical, Tallman, NY) and washed in phosphate-buffered solution. The tissues were then dehydrated and embedded in paraffin. Five-micrometer-thick sections were cut in the coronal plain and then stained with hematoxylin-eosin, safranin O, and picrosirius red. Three slides were made for each specimen. The specimens were evaluated by the 3 senior authors, who were blinded to the treatment group by use of polarized and non-polarized light. The organization of collagen tissue, new bone formation, vascularity at the tendon-bone interface, fibrocartilage at the tendon-bone interface, and collagen fiber continuity between tendon and bone tissue were evaluated. Picrosirius red staining was used for semiquantitative analysis of collagen content.[7,17] To evaluate the organization of collagenous tissue at the tendon-bone interface, sections were stained with picrosirius red and illuminated with monochromatic polarized light. Measurements were obtained by rotating the polarization plane until maximum brightness was obtained to control for variations in specimen orientation on the slide. To facilitate comparisons between groups, all tissues were embedded and cut in the same orientation and to a uniform thickness. The images were obtained with a Nikon Eclipse E800 light microscope (Nikon, Tokyo, Japan) that was interfaced to a CCD video camera mounted on an eyepiece tube. For all specimens, the images were taken under identical conditions of magnification and illumination during a single sitting. The images then underwent 8-bit digitization with ImageJ software (National Institutes of Health, Bethesda, MD) with a resolution of 640 × 480 pixels, yielding an image in which non-collagenous tissue was dark and collagen was depicted by gray scale from 1 to 255. Ten rectangular areas (50 μm × 50 μm) were measured, and the measurement of gray scale was performed with the ImageJ software. The values from the 10 rectangles were then averaged to obtain a value of average "brightness" per specimen, with the brighter specimens having more organized collagen.

Safranin O staining was used for semiquantitative analysis of the area of fibrocartilage at the insertion site. The area of fibrocartilage was carefully outlined and measured by use of ImageJ software (National Institutes of Health).

Biomechanical testing

Each rat shoulder was kept in a −80°C freezer until biomechanical testing was performed. The specimen was thawed at room temperature, and the humerus with attached supraspinatus was carefully dissected from surrounding tissues. The supraspinatus muscle was then bluntly removed from the supraspinatus tendon and set aside for determination of weight and volume. The cross-sectional area of the supraspinatus tendon was measured with a digital micrometer in the midsubstance of the tendon. The specimen was placed into a Materials Testing System (MTS Systems, Eden Prairie, MN) with a 45-N load cell to allow uniaxial tensile testing. The end of the tendon was secured in a screw grip by use of sandpaper and ethyl cyanoacrylate (Krazy Glue; Elmer's Products, Columbus, OH).[26] The humerus was then placed in a custom-designed vice grip that prevented fracture through the humeral physis. The specimen was preloaded to 0.10 N and then loaded to failure at a rate of 14 μm/s, corresponding to

approximately 0.4% strain. The load-to-failure data were recorded and stiffness calculated from the load-deformation curves by use of Sigma Plot 8.0 (SPSS, Chicago, IL). The site of graft failure (pullout from bone vs midsubstance rupture) was recorded.

Micro-CT

Bone density and new bone formation at the tendon insertion site on the greater tuberosity were assessed with micro-CT (eXplore Locus SP; GE Healthcare, London, Ontario, Canada). Micro-CT was done immediately after rats were killed, with the specimens in formalin for fixation. Each sample was placed in the holder surrounded by formalin and scanned at 80 V and 80 mA. The scans included a phantom containing air, saline solution, and a bone reference material for calibration of Hounsfield units to tissue mineral density. The images were thresholded to distinguish bone voxels by use of a global threshold for each specimen. After thresholding, the total bone mineral content, bone volume fraction (bone volume/total volume), and mineral distribution were calculated for a volume of interest at the greater tuberosity. The bone volume is the total number of thresholded bone voxels within the total volume of the volume of interest.

Muscle and tendon morphology assessment

Supraspinatus muscle volume and weight were measured at the time of biomechanical testing after blunt removal of the supraspinatus muscle from the tendon. The muscle weight was taken with a laboratory scale (model A-160; Thermo Fischer Scientific, Waltham, MA). The muscle volume was then measured by recording the amount of displaced water in a graduated cylinder. The width and height of the supraspinatus tendon were measured in the midsubstance of the tendon between the insertion site and muscle-tendon junction by use of a digital micrometer after removal of the muscle and before biomechanical testing.

Statistical analysis

The independent-sample Student t test was used to compare load to failure, tendon cross-sectional area, muscle weight and volume, and quantitative histology. A multivariate analysis was performed to evaluate the effect of all variables on the outcomes of the biomechanical analysis. Statistical analyses were performed with SPSS software, version 16.0 (SPSS, Chicago, IL), by a statistician.

Results

One rat died of anesthesia-related causes postoperatively and was replaced. There were no other postoperative complications. At the 8-week time point, the botulinum toxin A group had gained more weight than controls (68 g vs 51 g, $P < .02$); however, there was no difference in weight gain between the groups at 4 weeks and 24 weeks. There was no obvious difference in observed cage activity between groups. The botulinum toxin A group returned to a normal gait and resumed foreleg function at the same time postoperatively as the controls.

Table I Muscle weight of control and botulinum toxin A specimens

	Muscle weight (g)		
	4 wk*	8 wk*	24 wk
Control	0.52 ± 0.19	0.50 ± 0.07	0.53 ± 0.10
Botox	0.34 ± 0.10	0.31 ± 0.14	0.50 ± 0.43

* $P < .001$.

Table II Muscle volume of control and botulinum toxin A specimens

	Muscle volume (mL)		
	4 wk*	8 wk†	24 wk
Control	50 ± 18	51 ± 9	53 ± 10
Botox	35 ± 12	30 ± 13	43 ± 8

* $P < .01$.
† $P < .001$.

Gross observations at time of rat death

There was no evidence of gross disruption or failure to heal in any of the animals. In the 4- and 8-week botulinum toxin A groups, there were scar-like adhesions in the interval between the deltoid and supraspinatus. The supraspinatus muscle grossly showed decreased volume in the 4- and 8-week botulinum toxin A groups. At 24 weeks, there were no observable differences between the groups.

Muscle weight and volume

At 4 weeks, the muscle weight and volume were significantly greater in the controls than the botulinum toxin A group. This atrophy in the supraspinatus muscle was more pronounced at 8 weeks. By 24 weeks, there was no significant difference in the muscle weight or volume between groups. Data can be seen in Tables I and II. A significant difference in the cross-sectional area measurements of the supraspinatus tendon was only found between the control and botulinum toxin A groups at 8 weeks, with the tendons in the botulinum toxin A group being smaller than controls ($P < .01$).

Histologic analysis

At 4 weeks, the control specimens had less fibrocartilage and were less organized than the botulinum toxin A specimens, which all showed a tidemark (indicating better-organized interface tissue). In addition, the controls were more cellular and had increased vascularity compared with the botulinum toxin A group. At 8 weeks, the differences between the control and botulinum toxin A specimens were less pronounced, with the tendons becoming less cellular in both groups. By 24 weeks, both groups had well-aligned cells with an

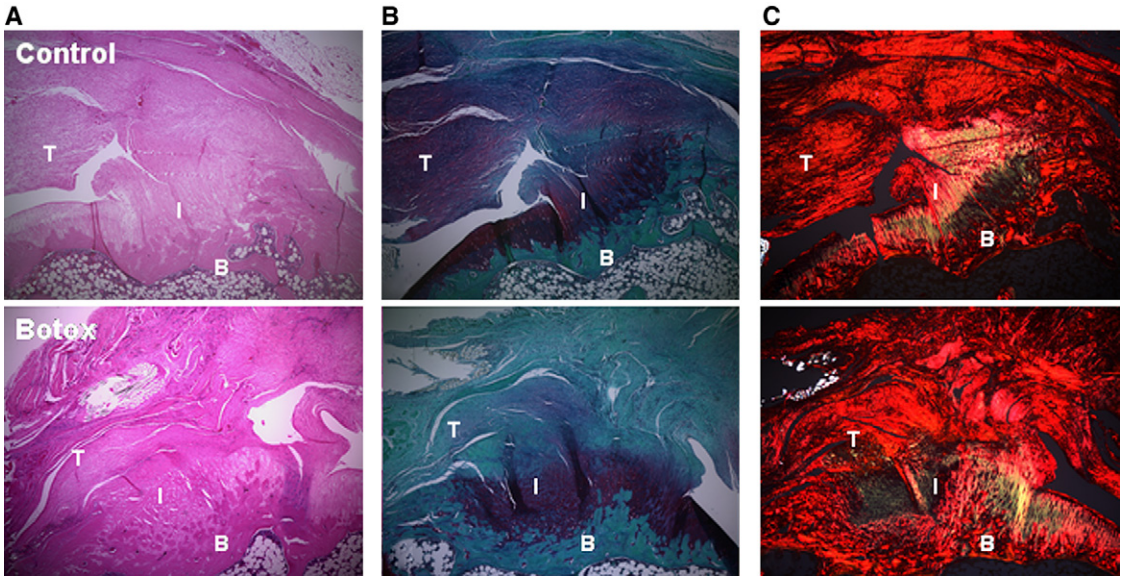

Figure 2 Hematoxylin-eosin (**A**), safranin O (**B**), and picrosirius red (**C**) images of control and botulinum toxin A specimens at 8 weeks, with less pronounced differences between groups and a decrease in cellularity in both groups. T, supraspinatus tendon; I, interface; B, bone.

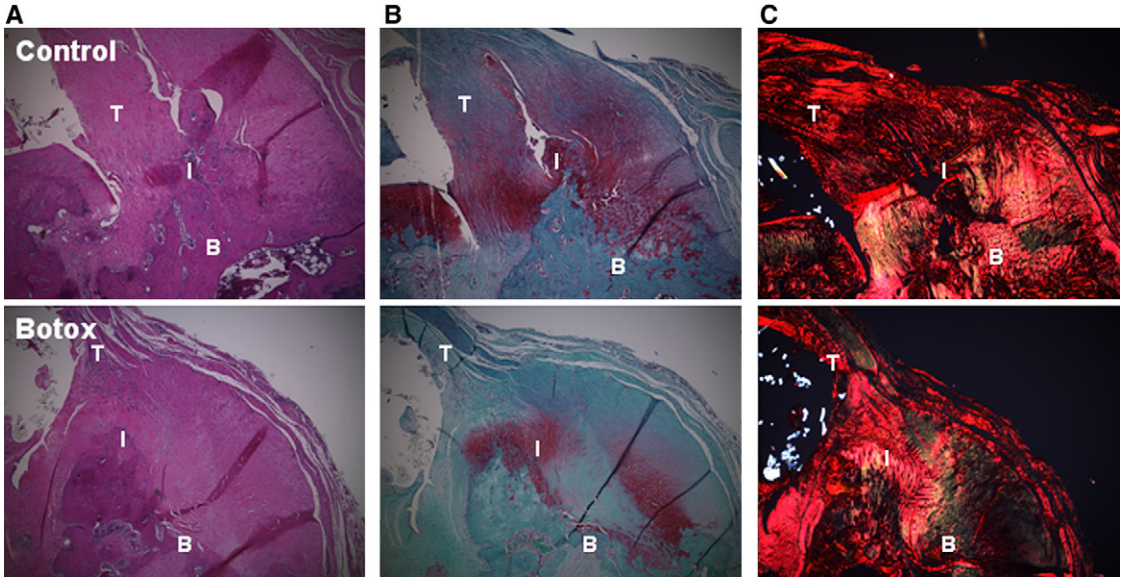

Figure 3 Hematoxylin-eosin (**A**), safranin O (**B**), and picrosirius red (**C**) images of control and botulinum toxin A specimens at 24 weeks, with both groups having well-aligned cells and an organized interface between the tendon and the bone. In both groups the bursal fibers of the supraspinatus tendons appeared to be better organized than the articular fibers. T, supraspinatus tendon; I, interface; B, bone.

organized interface between the tendon and the bone. In both groups the bursal (tension)—side fibers of the supraspinatus tendons were better organized than the articular-side fibers. Representative histologic images can be seen in Figures 1, 2, and 3. There was increased collagen birefringence in the botulinum toxin A group compared with controls at 4 weeks, indicating improved collagen maturity and organization ($P < .01$). There were no significant differences in the collagen fiber orientation in the 8- or 24-week groups (Fig. 4). The area of fibrocartilage was significantly less in the control group at 4 weeks. There was no difference in the area of fibrocartilage at 8 or 24 weeks (Fig. 5).

Biomechanical testing

There was no difference in tendon cross-sectional area at 4 weeks, but at 8 and 24 weeks, botulinum toxin A tendons had significantly less cross-sectional area than controls (Table III). At 4 weeks, 2 of 19 specimens in the control group and 2 of 19 in the botulinum toxin A group failed in

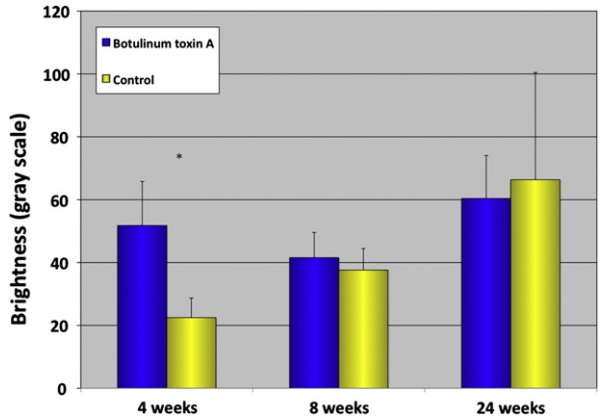

Figure 4 Graph of collagen fiber organization of control and botulinum toxin A specimens at 4, 8, and 24 weeks showing improved collagen fiber and maturity at 4 weeks in botulinum toxin A group.

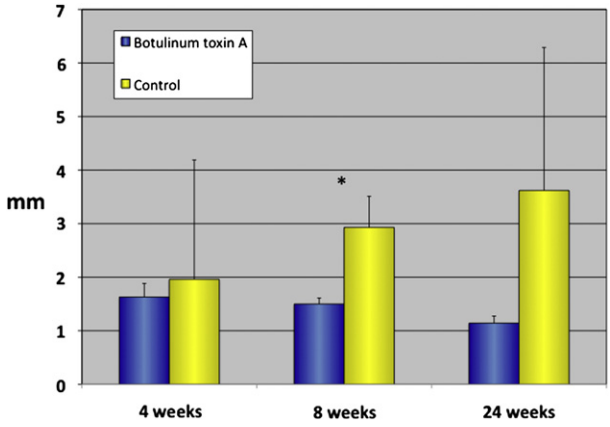

Figure 5 Graph of area of metachromasia at insertion site of control and botulinum toxin A specimens at 4, 8, and 24 weeks showing significantly more fibrocartilage in control group at 8 weeks.

the tendon midsubstance during load-to-failure testing, whereas the remainder failed at the tendon-to-bone interface. There was no significant difference in the load to failure at this time point between groups. At 8 weeks, midsubstance failure occurred in 4 controls and 1 botulinum toxin A specimen, and the remainder failed at the tendon-to-bone interface. The load to failure was 46.7 ± 14.2 N in the control group and 27.7 ± 6.2 N in the botulinum toxin A group ($P < .0001$). At 24 weeks, there were no differences in load to failure between the groups (43.1 ± 11.0 N vs 50.2 ± 13.8 N). There was no significant difference in failure stress at any time point. The load to failure for all the groups can be seen in Figure 6. A multiple regression analysis determined that both the use of botulinum toxin A and the area of the tendon were predictors of load to failure ($r^2 = 0.51$), with the use of botulinum toxin A showing an inverse relationship with load to failure and with area of the tendon showing a positive relationship.

Table III Cross-sectional area of control and botulinum toxin A specimens

	Tendon cross-sectional area (mm^2)		
	4 wk	8 wk*	24 wk†
Control	4.03 ± 1.45	5.90 ± 1.17	5.72 ± 0.90
Botox	4.03 ± 1.55	4.27 ± 1.40	4.83 ± 1.15

* $P < .001$.
† $P < .05$.

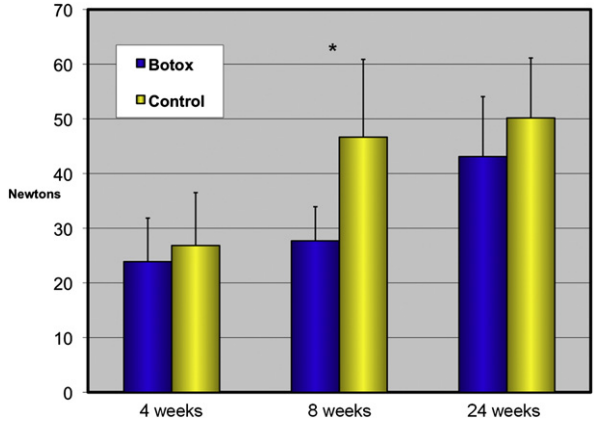

Figure 6 (**A**) Graph of load to failure (in newtons) of control and botulinum toxin A specimens at 4, 8, and 24 weeks showing significantly greater load to failure of control group at 8 weeks.

Micro-CT

Only cortical bone was evaluated because of the bony tunnels crossing through the humeral head disrupting the trabecular bone. The bone volume, total mineral content, and total mineral density were significantly lower in the botulinum toxin A group at the 8-week time point ($P < .05$). At 24 weeks, the only significant difference was in volume ($P < .05$), which was greater in the control specimens. The data for all time points can be seen in Table IV. Representative micro-CT images are shown in Figure 7.

Discussion

Our results supported our hypothesis that botulinum toxin A would lead to improved collagen organization. However, our data did not support our hypothesis that botulinum toxin A would result in improved attachment strength at the healing tendon-to-bone junction at early time points because the load to failure was not significantly different. This study shows that stress deprivation resulting from muscle paralysis in the healing rotator cuff tendon may be beneficial in the early healing period, as shown by the superior collagen fiber organization of the insertion site and tendon in the botulinum toxin A group. However, the reduction in load resulting from muscle paralysis led to

Table IV Micro-CT data for control and botulinum toxin A group

	Volume (mm^3)	Volume of bone (mm^3)	Total mineral content (mg)	Total mineral density (mg/mL)
4 wk				
Botox	4.210	3.336	2.665	798.3
Control	4.779	3.923	3.209	817.8
8 wk				
Botox	5.293*	4.584†	3.881†	846.4†
Control	5.728*	4.852†	4.210 †	867.7†
24 wk				
Botox	5.312†	4.6876	4.1412	883.5
Control	6.397†	5.556	4.845	872.0

* $P < .01$.
† $P < .05$.

disuse atrophy of the muscle and tendon and to a weaker insertion site at the 8-week time point. There was no significant difference in the strength of the insertion site at 24 weeks, when the muscle had regenerated and the effect of the paralysis from the botulinum toxin A was no longer present.

The negative effect of stress deprivation has been well demonstrated by in vivo[18,34,36] and in vitro studies.[8,15,23] A similar conclusion was reached by Galatz et al,[12] who showed decreased ultimate load to failure at 8 weeks and no difference in organization at that time point. Galatz et al found the worst results in animals that were treated with a combination of Botox and cast immobilization, suggesting that complete removal of load is detrimental to healing. However, in that study, decreased organization was reported at 3 weeks, which conflicts with the findings of the 4-week group in this study. In our study, the botulinum toxin A specimens had a clear tidemark and improved collagen fiber organization at 4 weeks. This study did not show a significant difference in load to failure or stiffness at 4 weeks, in contrast to Galatz et al. These differences could result from a difference in dosage, time point, or surgical technique. Furthermore, the control animals in their study received saline solution injection and were casted.

Our results contrast with a prior study that examined 3 postoperative regimens (shoulder immobilization in a cast, ad libitum cage activity, or exercise on a treadmill) after supraspinatus tendon repair in a rat model. Rats were killed at 2, 8, and 16 weeks. Shoulders that were immobilized showed superior structural, compositional, and biomechanical characteristics compared with the shoulders in the rats that were exercised.[32] A later study using the same model evaluated healing at 4 and 16 weeks and found that activity modification had no effect on the biomechanical properties at 4 weeks, but at 16 weeks, the decreased activity in the cast immobilization group had positive effects. There was less collagen fiber organization at 4 weeks in the exercised group but no differences at 16 weeks.[14] The authors reported that the cast was effective at ''preventing gross movement of the shoulder joint'' because the animals likely had micromotion within the casts. Thus, cast immobilization may allow for sufficient movement to load the tendon and the insertion to prevent disuse atrophy but still protect the healing site by preventing excessive motion and tension on the repair. When considered with the results of our study, it appears that both complete stress deprivation and excessive load are detrimental to tendon-to-bone healing. This has led to our hypothesis that controlled mechanical loading may be most effective if applied after an initial period of immobilization to allow the initiation of healing (delayed mechanical loading). The botulinum toxin A–induced muscle paralysis in our study appears to last too long, resulting in the adverse changes associated with prolonged disuse. A paralytic agent with a shorter duration of action may be beneficial in rotator cuff tendon repair.

The improved collagen fiber organization in the botulinum toxin A–treated animals in this study and in the cast-immobilized animals[32] suggests that intrinsic molecular signals may be more important than mechanical loading in directing the early histologic organization of the healing tendon-bone interface. Despite the histologic improvement at the healing interface, the biomechanical strength of the attachment was inferior. This may result from other alterations in the microscopic structure and composition of the healing tissue, such as collagen fibril diameters, collagen cross-links, or non-collagenous matrix proteins.

Significant decreases in bone volume, total mineral content, and total mineral density were seen in the 8-week botulinum toxin A group. Similar results were also seen in a study of the effect of muscle paralysis in the postnatal period on the development of the supraspinatus enthesis,[21] where there was a decrease in mineralized bone at 3, 4, and 8 weeks. Bony changes were also reported after botulinum toxin A administration into the supraspinatus, infraspinatus, and deltoid in postnatal mice. Continued paralysis led to bone and joint deformities including delayed mineralization, hypoplasia, and flattening of the humeral head.[31] Taken together, these results show that the removal of all

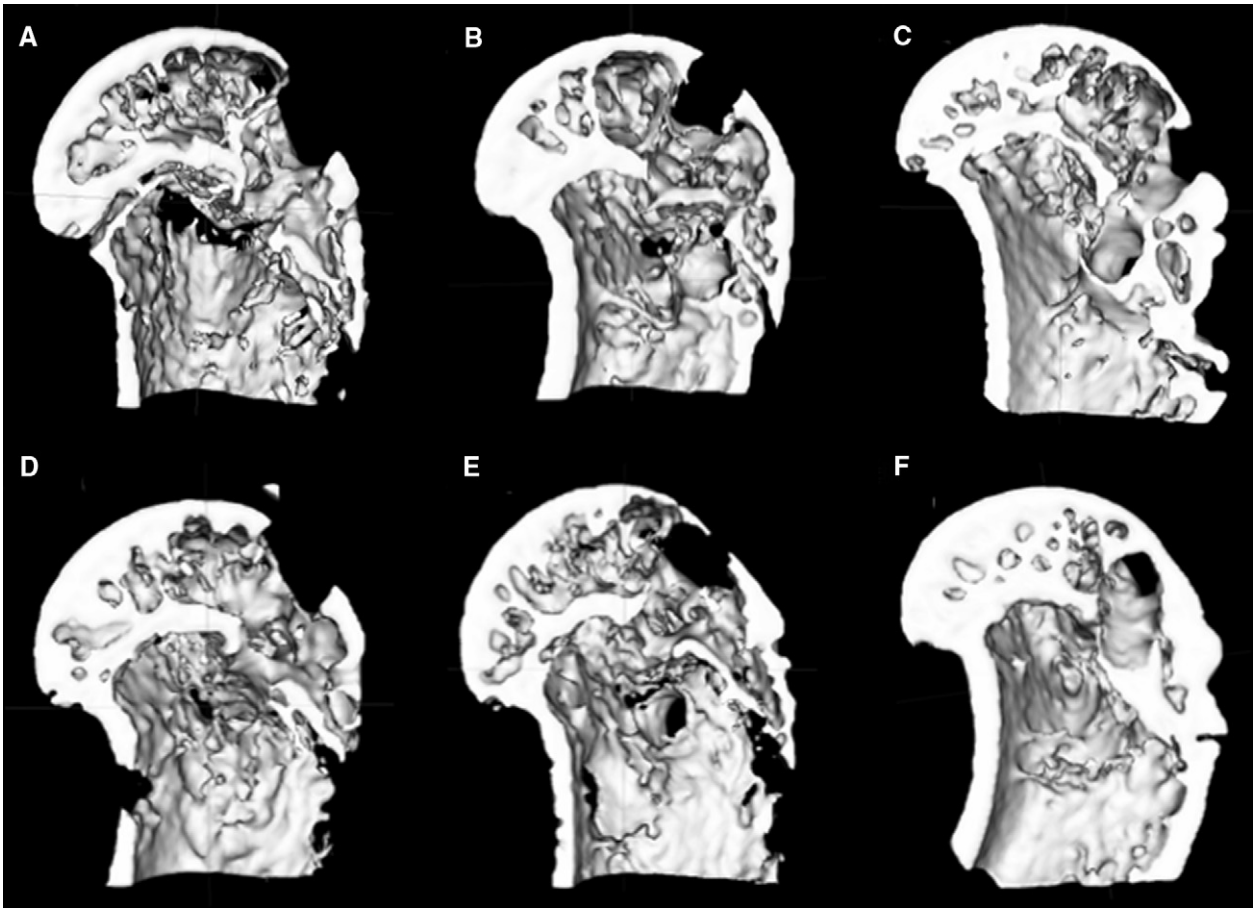

Figure 7 Representative micro-CT images of botulinum toxin A at 4 weeks (**A**), 8 weeks (**B**), and 24 weeks (**C**) and control specimens at 4 weeks (**D**), 8 weeks (**E**), and 24 weeks (**F**) depicting lower bone volume, total mineral content, and total mineral density in botulinum toxin A group at 8 weeks and increased bone volume in control specimens at 24 weeks.

load is detrimental to the healing enthesis. Support for the use of muscle paralysis to protect tendon repairs comes from a study in which botulinum toxin A was used to protect Achilles tendon repairs in a rat model.[25] In that study the treated muscles were unable to generate the tetanic force required to rupture the Achilles repair, thus protecting the repair. The spontaneous rupture rate of the Achilles was 3 times less at 1 week in the botulinum toxin A group, and the tendon rupture force was significantly higher in the botulinum toxin A group between 1 and 3 weeks after repair.[25] These findings highlight the potential positive effects of botulinum toxin A in an early healing model; however, later time points were not evaluated. In addition, the study evaluated tendon-to-tendon repair, in contrast to tendon-to-bone repair in the current study.

Our study has several limitations, including clear differences between rat and human rotator cuff healing. Rotator cuff tendon healing in the rodent model is rapid and less likely to fail, in contrast to humans.[7,11] Tendon healing in the rat model is largely complete by 8 weeks, whereas human tendon-to-bone healing requires at least 12 weeks. In addition, healing occurs in the rat despite loading of the repair site due to joint motion and activity and, as such, may not benefit from the reduction in strain on the supraspinatus tendon. In contrast, human failure rates are relatively high despite sling immobilization postoperatively. Therefore, the positive effect of removing load from the acutely repaired tendon in humans may outweigh the negative effects of stress deprivation. This study is also an acute repair model, whereas many rotator cuff tears in humans are chronic with degenerative tendinosis. Finally, we did not use a control group with saline solution injection into the muscle.

Conclusion

The results of this study suggest that removal of load on the healing tendon-bone interface leads to improved collagen fiber organization. However, the disuse atrophy in the muscle and resultant lack of any mechanical load adversely affect the strength of the repair. It appears that a low level of controlled force is beneficial for healing.

Further studies are necessary to investigate the potential positive effects of removing tension from an acutely repaired tendon. In addition, studies may also help to clarify the negative effects of the stress deprivation on the tendon-to-bone interface. Further insight into the effects of muscle paralysis on tendon-to-bone healing could come from study of earlier time points (1 or 2 weeks) and later time points when the reinnervation of the muscle is beginning to occur. Further studies are needed to determine whether botulinum toxin A can have a beneficial effect on the healing of tendon-to-bone repairs in humans. We are currently continuing our investigation in this area using an impaired-healing model in rats, where the reduction in strain at the repair site may show more beneficial effects.

Disclaimer

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