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Rotator cuff healing after continuous subacromial bupivacaine infusion: an in vivo rabbit study

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Abstract

Background—The objective of this study was to evaluate the effects of continuous subacromial bupivacaine infusion on supraspinatus muscle and rotator cuff tendon healing via gross, biomechanical, and histologic analyses.

Methods—Thirty-three New Zealand White rabbits underwent unilateral supraspinatus transection and rotator cuff repair (RCR). Rabbits were assigned to 1 of 3 groups: (1)RCR only, (2)RCR with continuous saline infusion for 48 hours, or (3)RCR with continuous 0.25% bupivacaine with epinephrine (1:200,000) infusion for 48 hours. Rabbits were sacrificed at either 2 (for histologic assessment) or 8 weeks post-operatively (for biomechanical and histologic assessment).

Results—Tensile testing showed significantly higher load to failure in intact tendons compared to repaired tendons ($p<0.01$); however, no statistical differences were detected among RCR only, RCR Saline, and RCR Bupivacaine groups. Histologically, the enthesis of repaired tendons showed increased cellularity and disorganized collagen fibers compared to intact tendons, with no differences between treatment groups. Muscle histology demonstrated scattered degenerative muscle fibers at 2 weeks in both RCR Saline and RCR Bupivacaine, but no degeneration was noted at 8 weeks.

Conclusions—The healing supraspinatus tendons exposed to bupivacaine infusion showed similar histologic and biomechanical characteristics compared to untreated and saline infused RCR groups. Muscle histology showed fiber damage at 2 weeks for both the saline and bupivacaine treated groups, with no apparent disruption at 8 weeks, suggesting a recovery process. Therefore, subacromial bupivacaine infusion in this rabbit rotator cuff model does not appear to impair muscle or tendon following acute injury and repair.

Level Of Evidence—Basic science study

Keywords

rotator cuff; myotoxicity; local anesthetic; bupivacaine; enthesis; subacromial

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Introduction

Post-surgical pain management has evolved to include continuous infusion pain pumps, which are commonly used to ameliorate pain by delivering local anesthetic directly to the affected area. Pain pumps, most often using bupivacaine in combination with epinephrine, are effective in decreasing post-operative pain[31,36] in the first 48 hours after surgery when pain is most severe. [20,37] However, complications associated with intra-articular bupivaciane infusion have been reported. Prolonged exposure to local anesthetic has been implicated as a cause of chondrolysis in several case series,[1,2,21,26,33,34] as well as in animal models[17,18] and *in vitro* work.[11,12,14,24,32] These recent findings recommended the abandonment of intra-articular placement of pain pump catheters.

While reports of post-operative chondrolysis have almost exclusively been in association with intra-articular infusion for glenohumeral joint procedures (e.g., labral repair) with an intact rotator cuff, the use of pain pump catheters within the subacromial space after rotator cuff repair has continued to be clinically utilized.[3,13,40] Some surgeons still advocate subacromial placement of the infusion catheter, suggesting that the drug predominately bathes the repaired tendon and bursae within a larger space compared to the glenohumeral joint. In this space it is allowed easier egress postoperatively and is associated with a larger postoperative hematoma, potentially reducing any chondrotoxic effect.

Subacromial placement of the infusion catheter may avoid devastating chondrolysis, but there are concerns regarding bupivacaine's effects on the surrounding soft tissues. Bupivacaine is toxic to both skeletal muscle and tendon fibroblasts,[10,29,39,47] thus raising concern that this toxicity may compromise rotator cuff tendon healing and/or muscle structure. Bupivacaine may also detrimentally affect fibroblast activity and proliferation, which is especially important in rotator cuff healing.[35] Watson et al,[39] showed that even dilute concentrations of bupivacaine for 30 minutes were toxic to tendon fibroblasts.

Myotoxicity resulting from local anesthetics is well established, as demonstrated in early studies of bupivacaine injection into the skeletal muscle of rats,[4,15,41] monkeys,[8] and humans.[41] Typical findings in this regard have included muscle fiber necrosis and infiltration of macrophages. With the increasing popularity of regional anesthesia, anesthesiologists are describing bupivacaine-induced myopathy associated with nerve blocks and other forms of local anesthetic injections. [28–30,43] Despite these studies, the available literature suggests that myotoxicity following injection with a local anesthetic is subclinical and reversible, likely due to short exposure time.[10,22,29,30,46,48] However, with the advent of continuous infusion pain pumps, it is presently unknown whether local anesthetic may cause more significant (i.e., irreversible) muscle damage due to prolonged exposure time to the muscle tissue.

The objective of the present study was to elucidate the *in vivo* effects of bupivacaine on supraspinatus muscle and rotator cuff tendon healing via gross, biomechanical, and histologic analyses. We utilized an acute model of rotator cuff (RC) injury and repair in rabbits to examine the healing responses at 2 and 8 weeks post-operatively. We hypothesized that bupivacaine does not impair rotator cuff muscle or tendon healing in a rabbit model.

Materials and Methods

Experimental Design

All protocols and procedures were approved by the authors' Institutional Animal Care and Use Committee. Thirty-three skeletally-mature, male New Zealand White rabbits

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approximately 4–5 months old at the time of surgery were randomized to one of the following three treatment groups (n=11 animals per group): unilateral rotator cuff repair with no drug treatment (RCR only), unilateral rotator cuff repair with infusion of saline (RCR Saline), or unilateral rotator cuff repair with infusion of bupivacaine (RCR Bupiv). Contralateral shoulders served as a fourth group, and received no surgery or drug treatment (Intact). Animals were further randomized to a 2 or 8 week post-operative endpoint. At the 2 week endpoint, supraspinatus tendon and muscle were histologically evaluated (n=2 per group, 3 analyzed specimens per animal). At 8 weeks post-op, supraspinatus tendon and muscle histology (n=2 per group, 3 analyzed specimens per animal) as well as supraspinatus tendon biomechanical properties (n=7 per group) were assessed.

Surgical Procedure

Animals were anesthetized, prepped, and an incision was made to expose the supraspinatus tendon insertion site. The supraspinatus tendon was identified approximately 1mm medial to its insertion, and a full-thickness complete transection of the tendon was created. The tendon was retracted medially, and two 3-0 Ethibond (Ethicon, Somerville, NJ) sutures were passed through the tendon and secured with a modified Mason Allen suture configuration. Two transosseus 0.75mm tunnels for the rotator cuff repair were drilled through the lateral aspect of the proximal humerus using a K-Wire Driver (Stryker, Kalamazoo, MI, USA). (Figure 1A) One end of each Ethibond suture was passed through each bone tunnel (one from the anterior and one from the posterior suture), and secured outside the bone tunnels on the lateral humerus. (Figure 1B) Following RCR, the shoulders of rabbits assigned to RCR Only (no infusion) were surgically closed. For rabbits assigned to saline or bupivacaine infusion, the syringe tip of a catheter was introduced into the subacromial space between the supraspinatus muscle and the overlying deltoid muscle. The catheter tip was secured in place using 6-0 Prolene sutured through a perfusion hole at the distal 1cm of the catheter, rotator cuff, and secured outside the skin. Catheter flanges were sutured to the skin with 3-0 nylon to prevent inadvertent displacement. Standard wound closure was performed. A pump jacket with a pouch (Lomir Biomedical Inc., Malone, NY) was placed on the rabbit to protect the sutures, catheter, and pump. (Figure 1C) In groups assigned to treatment with saline or bupivacaine, drug infusion consisted of either 0.9% normal saline with a pH of 5.9 (Hospira, Inc, Lake Forest, IL) or 0.25% bupivacaine hydrochloride and epinephrine (1:200,000) with a pH of 4.0 (Hospira, Inc, Lake Forest, IL). A 10ml Infu-Disk infusion pump (Med-E-Cell, San Diego, CA) set at a continuous fluid delivery rate of 0.21ml/hr was connected to a 20cm custom-designed 3.5 French silicone catheter with two perfusion holes at the distal 1cm and 2cm (Instech Solomon, Plymouth Meeting, PA). The pump was set to run for 48 hours, for a total of 10mL fluid delivered.[17] Pumps and catheters were removed after 48 hours of infusion. Fluid delivery was verified by measurement of the residual in the pump. Rabbits were housed in individual cages with no limitations of motion. They had access to food and water *ad libitum.* Rabbits received prophylactic cephazolin as well as buprenorphine as needed for pain management.

Tissue Analyses

At either 2 or 8 weeks after surgery, rabbits were sedated with ketamine/acepromazine (40mg/kg and 1mg/kg, respectively) and euthanized with an overdose of pentobarbital (200mg/kg). Shoulders were immediately dissected down to the rotator cuff and grossly inspected for inflammation, vascularity, and granulation tissue. Following excision of the infraspinatus and subscapularis muscles and tendons, the supraspinatus muscle was released nfrom its fossa, yielding a supraspinatus-humerus, muscle-tendon-bone complex.

Tendon Biomechanical Evaluation—For specimens designated for biomechanical testing, following tissue harvest, the supraspinatus muscle was removed to isolate the

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intramuscular tendon. For healing tendon specimens, care was taken not to compromise the integrity of the repair tissue regions during dissection. Prior to preparing specimens for mechanical testing, tissue width and thickness at the proximal tip of the fibrocartilaginous portion of the tendon insertion (area of repair tissue) was measured using a precision caliper (0.1mm resolution) and laser displacement sensor (model LK-G82, Keyence Corp., Woodcliff Lake, NJ) with 0.2 μm repeatability, respectively. (Figure 2A) Tendon cross-sectional area was computed as tendon width multiplied by its thickness.

Each humerus was potted within a PVC cylinder using acrylic cement (Isocryl, Lang Dental, Wheeling, IL, USA) and mounted to a custom fixture secured to the base of an electromechanical materials testing system (MTS Insight 5, Eden Prairie, MN). Each specimen was positioned such that the long axis of the tendon was aligned vertically (Figure 2B), in line with the test actuator. Four circular markers were affixed along the length of the tendon's bursal surface to digitally track regional tissue displacement during failure testing. To minimize potential tissue slippage during tensile testing, a cryoclamp[27] was used to securely grasp the intramuscular portion of the supraspinatus tendon 10mm proximal to the fibrocartilaginous portion of the tendon insertion. To minimize potential thermal effects on mechanical properties, the temperature along the entire length of tendon was maintained above 20°C (as verified using an infrared thermometer) using warm saline. Each specimen was preloaded at 5N for one minute and then elongated at a rate of 0.1 mm/sec until construct failure. Time, actuator displacement, and tensile load data were recorded at 48Hz using MTS TestWorks4 software. The observed mode of failure of each construct was noted and classified as tissue failure at gripping site, within the tendon substance, bone insertion, or bone fracture of the humeral shaft.

Tensile testing data was recorded synchronously with optical tissue deformation using a digital motion analysis system (Spica Technology Corporation, Maui, HI) comprised of a 1 megapixel digital video camera (Imperx model 1M48-L, 48 fps, Boca Raton, FL) and dedicated motion analysis software.[19,38] Using this approach, surface strain was computed for the following regions: humerus to tendon-bone insertion (Region 1), tendon-bone insertion to tip of the tendon fibrocartilage (Region 2), and tip of the fibrocartilage to myotendinous junction (a point 10mm further proximal) (Region 3) (Figure 2B). Using the tracking software, segment length (e.g., L1, L2, L3 for Regions 1, 2, and 3, respectively) was defined as the linear distance between the respective markers defining each region. Strain at failure was calculated as the percentage change in total length at maximum load (i.e., L1 + L2 + L3) relative to the total length at the preloaded state (i.e., $L_0 1 + L_0 2 + L_0 3$). For each region, deformation ratio was calculated as the change in segment length at maximum load relative to that in the preloaded state, normalized to the total deformation of the tendon-bone complex (e.g., deformation ratio for Region 1 was computed as $(L1-L_o1/[(L1-L_o1) + (L2-L_o2) + (L3-L_o3)])$.

From the load-displacement curve generated from each tensile test, the structural parameters maximum load, linear stiffness (steepest slope of the load-displacement curve spanning 30% of the data points collected between initiation of the load to failure test and the maximum load), and work to maximum load were computed.[38] Maximum stress was not reported, as not all specimens failed within the repair site.

Tendon Histology—Following removal of its adjoining muscle for histologic preparation, supraspinatus tendon–proximal humerus specimens were fixed in 10% neutral buffered formalin, decalcified in a formic acid/sodium citrate solution, dehydrated using graded alcohols, cleared, and paraffin embedded. Tendon-bone complexes were sectioned at 6 μm along the tendon's longitudinal axis and stained with hematoxylin and eosin (H+E). Three sections, at least 500 μm apart, were examined for each tissue specimen. Histological

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examination evaluated collagen fiber orientation, cellularity, granulation tissue deposition, vascularity, and the presence of inflammatory cells. Two blinded, independent examiners graded each of these characteristics on a scale of 0 to 2, with 0 corresponding to a normal specimen, 1 indicating minimal differences compared to a normal intact tendon, and 2 representing major changes compared to a normal intact specimen.

Muscle Histology—Each supraspinatus muscle was divided longitudinally into thirds and the portion nearest the glenohumeral joint (distal) was used for muscle histologic analysis. Muscle was fixed in 10% neutral buffered formalin, dehydrated, cleared and paraffin embedded. Tissues were sectioned transversely at 6 μm and stained with hematoxylin and eosin (H+E). Three random muscle section per specimen were scored by two blinded, independent examiners as described by Benoit et al[5], with 0 corresponding to no fiber damage, 1 indicating localized and/or sparsely scattered fiber destruction, 2 representing more extensive necrosis after major connective tissue planes and involving numerous muscle fascicles, and 3 reflecting destruction of essentially the entire muscle mass. Specimens were further examined by a musculoskeletal anatomist and a trained pathologist to assess for the presence of inflammatory cells, irregularly shaped muscle fibers, and degenerating or regenerating muscle fibers.

Statistical Analyses

Biomechanical data were initially assessed using Bartlett's test to confirm normality; on the basis of these results, comparisons across treatment groups were completed using a one-way analysis of variance (ANOVA). When the statistical factor of treatment was found to be significant, a Student-Newman-Keuls (SNK) multiple comparisons *post hoc* test was utilized to determine pairwise differences among groups. Analyses were performed with a significance level set at $p<0.05$ using GraphPad Prism 5 software (La Jolla, CA). In addition, post-hoc power analyses of the biomechanical outcomes were conducted using G*Power 3 (www.psycho.uni-duesseldorf.de/aap/projects/gpower).

Results

Gross Evaluation

Two weeks post-operatively, all rabbits that had been treated with infusion, whether saline or bupivacaine, had significant fluid accumulation around the shoulder, with most rabbits having a moderately sized seroma. Rabbits receiving RCR Only had no fluid collection. While all repairs were intact at necropsy, there was dense 'scar' at the insertion site for all groups. Eight weeks post-operatively, scar tissue was still present, but there was no fluid accumulation, as had been seen in the 2 week group. No necrotic tissue was noted.

Rotator Cuff Tendon Biomechanics

Three specimens were removed from analysis (one from the RCR Bupivacaine group, two from Intact group) due to slippage within the grip during pull to failure testing. The mean cross-sectional area of the repair tissue in the RCR Only group was greater ($p<0.05$) than at the corresponding location of intact specimens. Statistically, no other anatomical differences were noted among groups.

Tensile testing—Maximum load to failure, stiffness, and work to maximum load exhibited significantly higher values in the Intact group compared to RCR only, RCR Saline, and RCR Bupivacaine. (Table I)

Total strain was higher for RCR Only compared to Intact and RCR Saline ($p<0.05$) (Table I). Deformation ratios at maximum load, used to characterize relative regional contributions

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to the total deformation, were similar between all treatments groups. The Intact specimens showed a higher deformation ratio in the myotendinous junction (Region 3) compared to each of the repaired constructs. Further, the region of intact tendons corresponding to the region of repair tissue in healing specimens (Region 2) had lower deformation ratios compared to RCR Only and RCR Saline, ($p<0.05$) with a similar trend to RCR Bupivacaine. (Table II)

Failure Mode—Intact specimens failed at the base of the cryogrip. When tested to ultimate failure, the three treatment groups each experienced failures at the repair tissue or insertion, with one specimen failing as a bone avulsion at the shaft of the humerus near the potting cement. (Figure 3) Overall, there did not appear to be a difference in the frequency of failure modes between any of the RCR groups, as all 3 groups included a number of specimens with failures in the soft tissue, either at the insertion or within the repair tissue.

Rotator Cuff Histology

2 weeks Post-op—Two weeks following surgery, intact specimens displayed the four-zone direct insertion of bone, mineralized fibrocartilage, unmineralized fibrocartilage, and tendon. (Figure 4A) Fibrocartilage could be observed in all histologic sections, transitioning to tendon with well-aligned fibers.

All specimens that underwent RCR, regardless of infusion status, showed disruption of normal fiber orientation. As predicted from the large amount of repair tissue seen at gross dissection, the healing insertion site included tendon approximation to the remaining fibrocartilage stump as well as tendon to bone. At the interface between tendon and bone, remodeling was seen, with proliferation of fibrocartilaginous cells. Areas of cartilaginous cells were especially abundant near the surgically created bone tunnels. (Figure 4B–C) Local areas of inflammation were seen in the healing tendon as well as increased vascularity in repaired specimens. There were no gaps in any of the specimens. Necrotic tissue was seen in all samples undergoing repair, most often at the site of tendon transection or at the tendon-suture interfaces. No apparent differences were noted between any of the three groups.

8 weeks Post-op—Specimens in the RCR groups showed no inflammatory cells at 8 weeks. The collagen fibers were better oriented and cellularity was normal in most samples. (Figure 4D–E) There were no noted areas of increased vascularization. Also, necrotic tissue was not as prevalent as in the two weeks samples, even at areas where the supraspinatus transection could be identified.

Comparison of 2 and 8 week post-op specimens revealed differences in histologic appearance with improvements over time. At 8 weeks post-op, fibers were organized as parallel collagen bundles. Cellularity had decreased, and the vascularity seen at 2 weeks was no longer present.

Semi-quantitative analysis of specimens at both 2 and 8 weeks post-surgery did not reveal apparent differences between repair groups ($p<0.05$).

Muscle Histology

2 weeks Post-op—Muscle sections from (contralateral) intact rotator cuffs were homogenously stained with fibers of similar size, as determined by transverse sections. (Figure 5A) Muscle specimens of rabbits in the three repair groups were similar to Intact. (Figure 5B) There were no areas of muscle necrosis or fiber destruction. Saline and bupivacaine infused muscles showed edema, as muscle fascicles were often separated by

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large amounts of void space. Additionally, a few degenerative fibers were noted in both RCR Saline and RCR Bupivacaine groups. (Figure 5C–D)

8 weeks Post-op—All repaired groups also showed homogeneously stained fibers devoid of inflammation or necrotic tissue. (Figure 5E–G) In contrast to the 2 week findings, however, no degenerative muscle fibers were noted. (Figure 5F–G)

Assessment by semi-quantitative analysis revealed minimal muscle damage in any of the specimen groups at both 2 and 8 weeks post-operative, and there were no differences between repair groups ($p<0.05$).

Discussion

As previous studies have demonstrated myotoxicity and fibroblast toxicity following administration of local anesthetic, concern exists regarding bupivacaine's effects on muscle tissue and tendon healing. In the current study, at 2 and 8 weeks following supraspinatus tendon transection, RCR, and infusion with bupivacaine, the supraspinatus muscle showed few differences compared to intact muscle at 2 weeks, with no differences at 8 weeks. Further, rotator cuff tendon healing did not appear to be compromised by bupivacaine infusion.

Local anesthetics are well documented as a cause of myotoxicity,[4,5,8,15,30,41,43–47] shown with both single or series of injections as well as with continuous infusions. With the increased frequency of continuous local anesthetic infusions for regional pain control,[16] myotoxicity resulting form prolonged local anesthetic exposure is the topic of recent studies, especially in the field of anesthesia. Padera et al,[30] evaluated muscle tissue in rats after a sciatic nerve block utilizing sustained release bupivacaine microparticles. The particles allowed for sustainability of the local anesthetic, and authors showed that myotoxicity is related to duration of exposure, noting that even low concentrations of bupivacaine is myotoxic. Zink et al[47] evaluated the effects of prolonged exposure of ropivacaine and bupivacaine on skeletal muscle tissue. Femoral nerve catheters were placed within the nerve sheaths of minipigs and randomized to treatment with a saline, ropivacaine, or bupivacaine injection followed by continuous infusion of the drug for six hours. On immediate histologic analysis, muscle in both bupivacaine and ropivacaine treated tissue had interstitial edema, fiber vacuolation, condensed myofibrils, and necrotic cells, with bupivacaine showing more severe damage. Bupivacaine, but not ropivacaine, also induced apoptosis. Further, Zhang et al[43] reported concentration-dependent bupivacaine myotoxicity in rabbit extraoccular muscle. The authors shows myonecrosis and degeneration at 5 days after injection with the highest bupivacaine concentration (0.75%) followed by late-stage scar formation at one month. However, no long term effects were observed with bupivacaine concentrations of 0.38% or 0.19%.

Bupivacaine has also been suggested to be detrimental to fibroblasts. A recent study[39] examined the influence of 0.25% bupivacaine, 0.25% bupivacaine and epinephrine, Naropin (2% ropivicaine), and 1% lidocaine, each diluted in 0.9% saline, on cultured rat synovial fibroblasts. The authors reported that prolonged (i.e., 30 minute) contact with dilute (1:32) bupivacaine is toxic to fibroblasts. Despite the preliminary nature of the latter findings, in absence of other related data, there may exist concerns regarding whether bupivacaine impairs tendon healing, particularly when considering the vital role of fibroblastic activity in rotator cuff healing.[25,35] Further, Scherb et al[35] examined the effects of bupivacaine on cultured tenocytes. The authors found that bupivacaine decreased cell proliferation and production of collagen and proteoglycans in healthy human tenocytes.

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While *in vitro* results suggest bupivacaine's adverse effects, our study offers an *in vivo* setting that is more applicable to a clinical situation. In our rabbit model, histologic characteristics at 8 weeks post-operatively were similar compared to untreated and saline infused RCR groups. In all specimens, regardless of treatment group, the insertion site architecture remained disorganized at 8 weeks, although histologic appearance generally improved for the repaired specimens from the 2 to 8 week endpoints. Tensile testing at 8 week post-op showed intact specimens to be stronger than repaired tendons. However, there were no differences in the biomechanical properties among the three tendon repair groups, each of which predictably failed at a lower mean load than that of the intact specimens.

To further investigate the regional components of the rotator cuff involved in repair, we quantitatively compared three tissue regions with regard to optical deformation characteristics. (Table 2) Intact specimens showed a higher deformation ratio at the myotendinous region, and these tendons failed at the clamp. Conversely, repaired tendons had similar or lower deformation ratios of the myotendinous region compared to the repair tissue region, and these repaired specimens, regardless of treatment group, were more likely to fail within the soft tissue. These results suggest that under conditions of uniaxial tendon loading to failure, the repair tissue and myotendinous junction are the mechanically weaker areas of the tendon-bone complex, as their relative deformation contributions were the highest at rupture. Importantly, there were no significant deformational differences between any of the repair groups, suggesting that bupivacaine does not change the regional healing process.

In the present study, although scattered degenerative muscle fibers were noted at 2 weeks, the lack of myotoxicity at 8 weeks may be due to a number of factors. Most evaluations of myotoxicity have examined short endpoints (hours to days) *in vitro*. The lack of necrosis and inflammation in the present study may indicate that any incurred muscle damage had mostly resolved prior to the 2 week endpoint. Further, as drug delivery consisted of a constant infusion over the supraspinatus, the muscle may have been protected by surrounding tissues. Overall, these results suggest that bupivacaine does not have detrimental effects to the muscle beyond the short-term.

Tendon biomechanical properties are the primary outcome in this study, and post-hoc power analyses of data from the three repair groups revealed that statistical power ranged from 9 to 31% for the mechanical parameters reported in Table 1; the corresponding number of animals required to achieve 80% power for these metrics ranged from 20 to 117 per repair group. Sample size for the biomechanical analysis is similar to other rabbit rotator cuff repair studies. [6,9,23,27,42] We chose to investigate histologic findings as a complement to the current study, though we recognize that further studies with a larger sample size are likely required to confirm the latter findings.

Further, although the present study evaluated a short and intermediate endpoint, future studies assessing a greater number of time points would offer more information about the temporal effects of myotoxicity. As the muscle histologic sections showed evidence of regenerating muscle fibers, bupivacaine may have caused damage in hours to days after exposure, with a reparative process occurring immediately following. It would be interesting to determine whether bupivacaine infusion causes an inflammatory response or tissue necrosis immediately after infusion.

To remain consistent with the clinical practice of bupivacaine infusion in conjunction with epinephrine, this study examined a bupivacaine plus epinephrine solution rather than a pure bupivacaine infusion. Although this is a limitation of the study, previous studies have shown that local anesthetic has the same effect on soft tissue with or without epinephrine.[7,17]

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Furthermore, although bupivacaine is the local anesthetic of choice in pain pump infusions, other local anesthetics, such as lidocaine and ropivacaine, should be assessed to determine their effects of rotator cuff healing. Varying potencies and half-lives of different local anesthetics may produce a different response. Finally, this study lacked a control group utilizing RCR and catheter placement without drug delivery to rule out catheter-associated damage. While the catheters were small (3.5Fr) and placed in the muscle tissue where mechanical trauma is unlikely, this cannot be ruled out as a source of potential muscle damage or detrimental tendon healing.

Conclusions

Subacromial bupivacaine infusion introduces concern regarding bupivacaine's effects on muscle tissue and tendon healing, as previous *in vivo* studies have demonstrated myotoxicity following administration of local anesthetic as well as bupivacaine's *in vitro* toxicity to fibroblasts.In the present study of a rabbit model of RCR at 2 and 8 weeks post-operatively, the healing supraspinatus tendons exposed to bupivacaine infusion showed similar histologic and biomechanical characteristics compared to untreated and saline infused RCR groups. Muscle histology showed fiber damage at 2 weeks for both the saline and bupivacaine treated groups, with no apparent disruption at 8 weeks, suggesting a recovery process. Therefore, subacromial bupivacaine infusion in this rabbit rotator cuff model does not appear to impair muscle or tendon following acute injury and repair.

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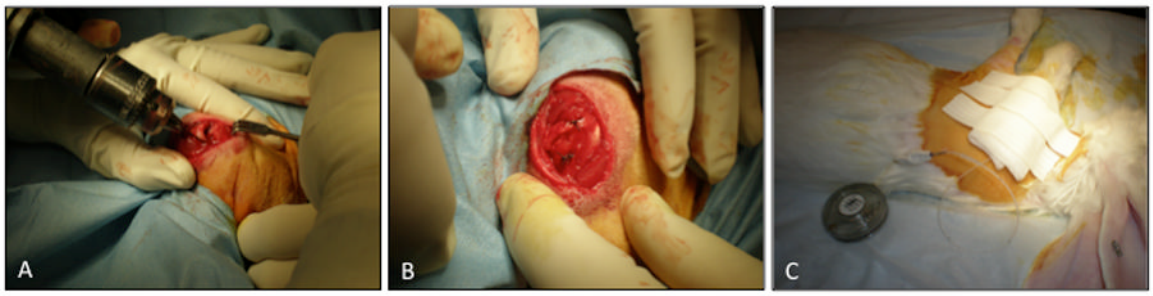

Figure 1.

Figure 1A–C. Unilateral rotator cuff transection and repair**. A.** Drilling of the transosseous tunnels for RCR. **B.** Completed RCR, just prior to placement of the subacromial catheter. **C.** Dressings in place with catheter attached to infusion pump.

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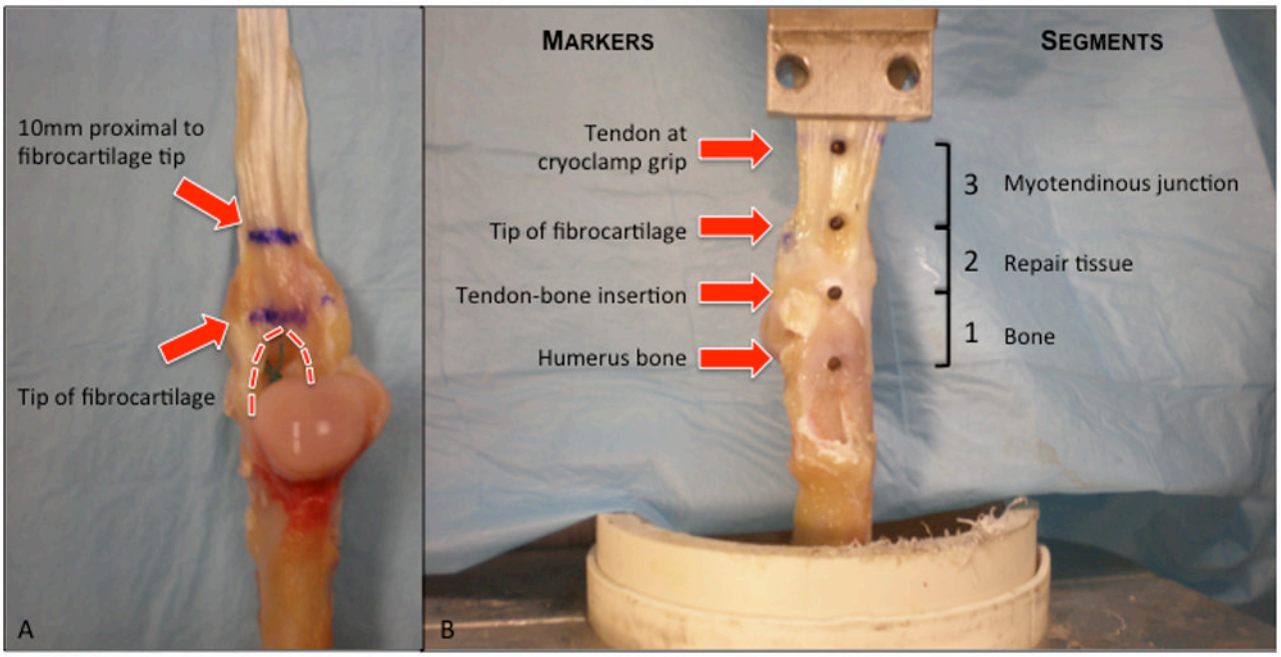

Figure 2.

A. Articular side of tendon-bone complex, showing the fibrocartilage (red dashed lines), and 10mm proximal to the fibrocartilage tip (site of cryogrip attachment) **B.** Markers and segments used for optical tissue deformation measurements. Shown is an intact tendon with 4 markers and 3 segments.

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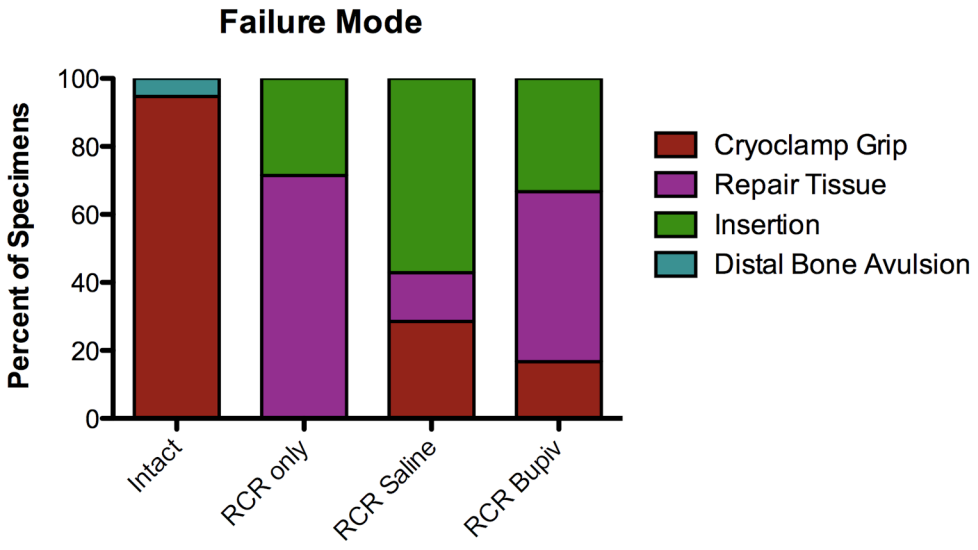

Figure 3.
Location of Failure during tensile testing.

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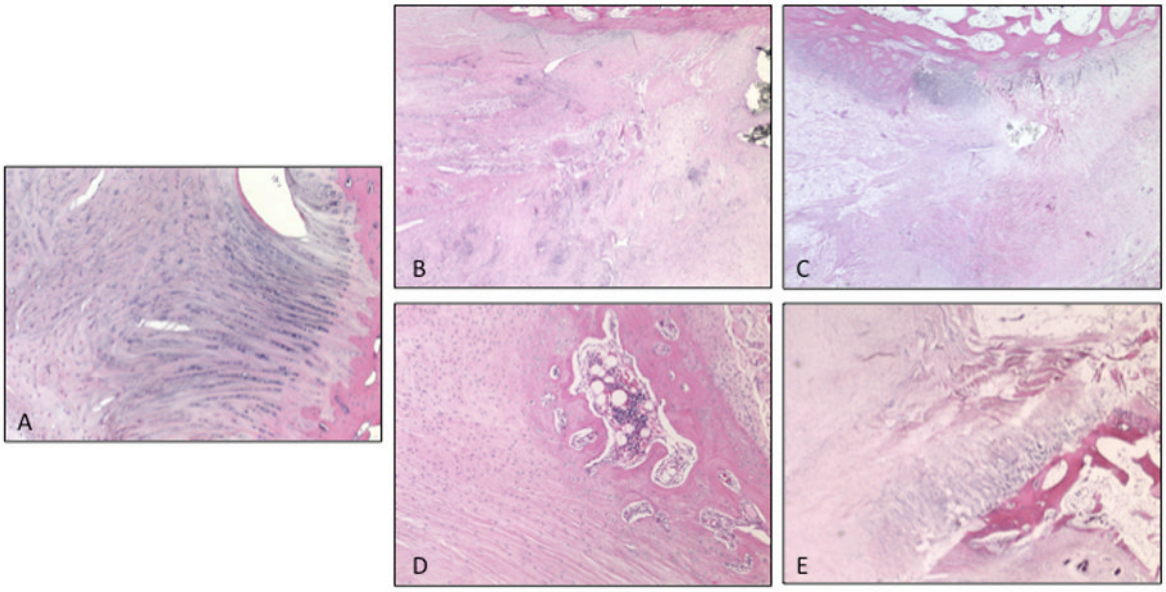

Figure 4.

Rotator Cuff Histology. **A**, Normal tendon-bone interface (Intact group). **B–C,** Tendon insertion longitudinal sections at 2 weeks post-op. **B**, RCR Saline. The interface is highly cellular, with areas of muscle destruction, and increased vasculature. Suture is seen in the top right corner. **C**, RCR Bupiv. At the interface between tendon and bone, remodeling was seen, with proliferation of fibrocartilaginous cells. **D–E,** Tendon insertion longitudinal sections at 8 weeks post-op. **D**, RCR Saline. The tendon–bone interface shows new bone formation, with collagen fibers better oriented than at 2 weeks post-op. **E**, RCR Bupiv. The tendon-bone interface is beginning to restore, with better orientation of collagen fibers. No inflammatory cells or necrosis is noted. (hematoxylin and eosin; magnification 20X)

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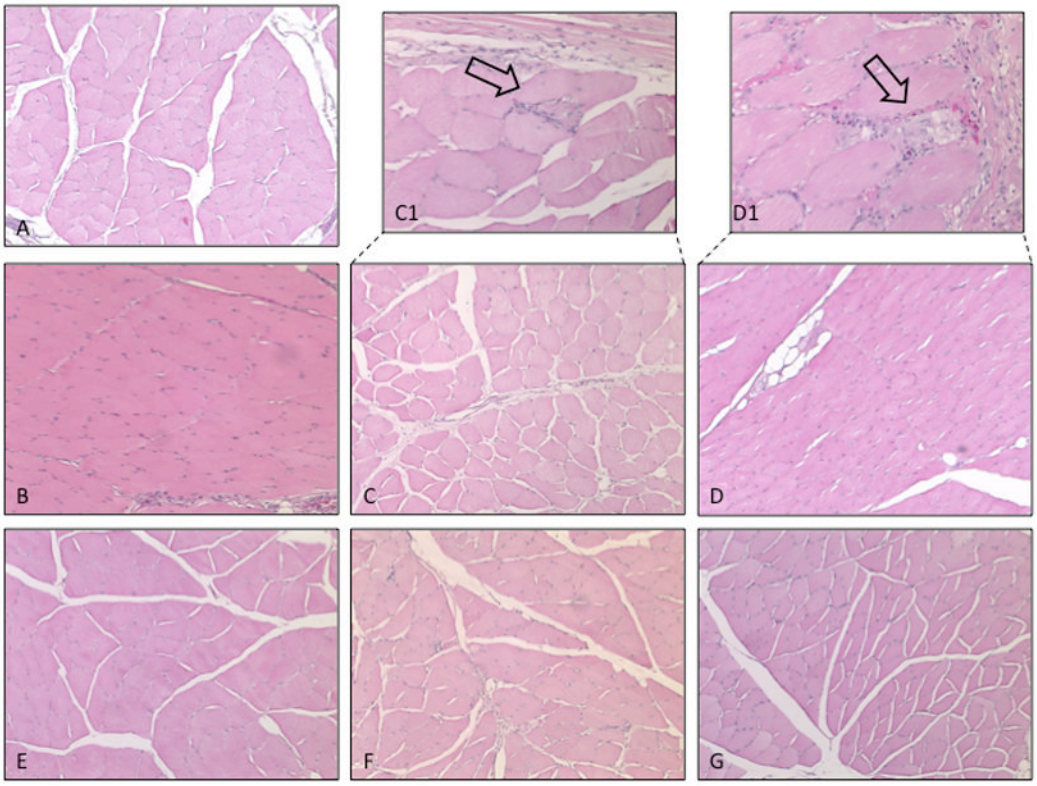

Figure 5.

Muscle Histology. **A–D,** Muscle tissue transverse section at 2 weeks post-op. **A.** Intact. **B.** RCR Only. **C, C1.** RCR Saline. **D, D1.** RCR Bupivacaine. Scarce degenerating muscle fibers were found for both RCR Saline and RCR Bupiv (open arrows). **E–G**, Muscle tissue transverse section at 8 weeks post-op. **E.** RCR Only. **F.** RCR Saline. **G.** RCR Bupivacaine. Normal muscle fibers without inflammation or damaged tissue. (hematoxylin and eosin; magnification for A, B, C, D, E, F, G is 100X, magnification for C1 and D1 is 200X)

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Table I

Geometric and Biomechanical Properties. Intact specimens showed significantly higher maximum load to failure, stiffness, and work to maximum load compared to repaired tendons.

	Intact	RCR only	RCR Saline	RCR Bupiv
Cross-sectional Area (mm^2)	32.0 ± 11.9	52.6 ±13.3 *	41.6 ± 17.1	46.1 ± 17.4
Maximum Load (N)	374.5 ± 43.3 **	222.1 ± 58.2	244.9 ± 64.2	228.8 ± 51.9
Stiffness (N/mm)	111.8 ± 28.3 **	57.2 ± 26.1	74.2 ± 20.5	77.7 ± 31.4
Work to Maximum Load (N-mm)	1843 ± 708 **	913 ± 411	789 ± 334	596 ± 218
Total Strain	0.080 ± 0.017 ***	0.131 ± 0.042	0.078 ± 0.024	0.093 ± 0.027

* Mean cross-sectional area of the repair tissue in the RCR Only group was greater ($p<0.05$) than at the corresponding location of intact specimens.

** Mean values for Intact group were significantly greater than those of the three repair groups. There were no significant differences among the three repair groups.

*** Total strain was higher for RCR Only compared to Intact and RCR Saline ($p<0.05$).

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Table II

Deformation Ratios at failure for the tissue regions shown in Figure 1B.

Segment	Intact	RCR Only	RCR Saline	RCR Bupiv	p-value
3	0.70 ± 0.10	0.25 ± 0.11	0.40 ± 0.16	0.46 ± 0.24	<0.05[b]
2	0.22 ± 0.09	0.52 ± 0.18	0.46 ± 0.17	0.36 ± 0.18	<0.05[a]
1	0.07 ± 0.04	0.23 ± 0.21	0.14 ± 0.10	0.18 ± 0.29	>0.05
p-value	<0.05 *	<0.05 **	<0.05 ***	>0.05	

[a] Segment 2: Significant difference between Intact and RCR Only; Intact and RCR Saline;

[b] Segment 3: Significant difference between Intact and each of the three RCR groups.

* Intact: Significant difference between all segments

** RCR Only: Significant difference between 1 and 2; 2 and 3

*** RCR Saline: Significant difference between 1 and 2; 1 and 3