J Shoulder Elbow Surg (2017) ■■, ■■–■■

ELSEVIER

Journal of Shoulder and Elbow Surgery

www.elsevier.com/locate/ymse

ORIGINAL ARTICLE

Subacromial corticosteroid injections transiently decrease suture anchor pullout strength: biomechanical studies in rats

Oleg Dolkart, PhD[a,1,*], Ofir Chechik, MD[a,1], Assaf Bivas, MD[a], Tamar Brosh, PhD[b], Michael Drexler, MD[a], Zachary Weinerman, MD[a], Eran Maman, MD[a]

[a]*Shoulder Unit, Division of Orthopaedic Surgery, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

[b]*Biomechanics Laboratory, School of Dental Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

Background: Arthroscopic rotator cuff (RC) repair incorporates suture anchors to secure torn RC tendons to the greater tuberosity (GT) bone. RC repair strength depends on the anchor-bone interface and on the quality of the GT. We evaluated the effect of single and multiple corticosteroid injections on the pullout strength of suture anchors.

Methods: Fifty rats were divided into those receiving saline solution injection (control group), a single methylprednisolone acetate (MTA) injection (MTA1 group), or 3 once-weekly MTA injections (MTA3 group). Rats were killed humanely at 1 or 4 weeks after the last injection. A mini–suture anchor was inserted into the humeral head through the GT. Specimens were tested biomechanically.

Results: At 1 week after the last injection, the mean maximal pullout strength was significantly reduced in the MTA1 group (63.5%) and MTA3 group (56%) compared with the control group ($P < .05$ for both). Mean stiffness decreased significantly in both treatment groups compared with controls ($P < .05$). At 4 weeks after the last injection, there was a significant increase in the mean maximal pullout strength after single and triple MTA injections compared with values recorded at the 1-week time point ($P < .05$). At 4 weeks, the mean maximal pullout strength after a single MTA injection was 92.8% of the pullout strength measured in the control group.

Conclusions: We showed a significant detrimental effect of corticosteroid exposure on the pullout strength of a suture anchor at 1 week. However, this effect was transient and resolved within a relatively short period. These findings indicate that a waiting period is required between subacromial corticosteroid injection and RC repair surgery that involves the use of suture anchors.

Level of evidence: Basic Science Study; Biomechanics; Animal Model

Keywords: Suture anchors; greater tuberosity; corticosteroids; biomechanics; rats; detrimental effects; subacromial injection; rotator cuff repair

Rotator cuff (RC) tears constitute a widespread problem and one that can cause significant pain and disability in 80% of persons aged over 70 years.[13,17] The ages of patients undergoing RC repair may vary from 28 to 83 years, with an average of 56 years.[5] Arthroscopic RC repair has become

This study was approved by the Institutional Animal Care and Use Committee.

*Reprint requests: Oleg Dolkart, PhD, Orthopedic Surgery Division, Tel Aviv Medical Center, 6 Weizman Street, Tel Aviv 6423906, Israel.

E-mail address: dolkarto@gmail.com (O. Dolkart).

[1]These authors contributed equally to this work.

1058-2746/$ - see front matter © 2017 Journal of Shoulder and Elbow Surgery Board of Trustees. All rights reserved.
http://dx.doi.org/10.1016/j.jse.2017.05.013

the established method of reconstruction. It involves the use of suture anchors to secure the torn RC tendons to the greater tuberosity (GT) bone. Several biomechanical studies have identified the most common mechanisms of suture anchor failure. It is believed that the most common location for failure is at the tendon-suture interface[4]; however, some studies have reported suture anchor failure at the anchor-bone interface as well.[11] The strength of the RC repair may be dependent on the interface between the anchor and the quality of the bone (ie, bone mineral density [BMD]) into which the anchor is placed.[9]

Single or multiple corticosteroid injections are often prescribed during treatment of chronic tendon disorders[10,12] because of their effective anti-inflammatory and pain-relieving properties. The many adverse effects of the drugs are often overlooked. One of the main limitations of glucocorticoid therapy is the harmful effect on the skeletal system. Glucocorticoids can cause bone loss (ie, osteoporosis) and fractures, which are collectively referred to as "glucocorticoid-induced osteoporosis."[2,4] To avoid the potential negative effects on postoperative outcomes, some orthopedic surgeons do not perform corticosteroid injections. One recently published study showed that both single and multiple corticosteroid injections have the potential to induce humeral head osteopenia in a rat model of RC tear.[10] These results are of some concern because surgical RC repair involving suture anchors relies on the fixation of anchors within the tuberosity. Decreased bone density can, therefore, result in pullout of the anchors from the bone, leading to early failure of the RC repair.

This study was designed to evaluate the effect of single and multiple corticosteroid injections on the pullout strength of suture anchors in rats. We hypothesized that corticosteroid exposure would have a deleterious effect on the biomechanical properties of the GT bone, resulting in decreased suture anchor pullout strength.

Methods

Fifty adult male Wistar rats (body weight of 250-300 g; Harlan Laboratories, Jerusalem, Israel) were used in all of the experiments. The animals were maintained on a 12-hour light–12-hour dark cycle at 21°C to 22°C and acclimatized for 7 days before the experiments. The rats were allowed ad libitum access to food and water.

Study groups and treatments

The 50 rats were randomly assigned into 1 of 3 groups: injection of normal saline solution (control group, n = 10), single methylprednisolone acetate (MTA) injection (MTA1 group, n = 20), or 3 once-weekly MTA injections (MTA3 group, n = 20) (Fig. 1). The concentration of a single MTA dose injected into the subacromial space was 0.6 mg/kg. (It should be noted that the MTA dose routinely injected in patients is 40 mg. Assuming a patient's weight to be approximately 70 kg, the MTA concentration will be 0.66 mg/kg, which is the concentration of MTA used in our study, equivalent to a human dose.) Normal saline solution was injected into the subacromial space of the rats in the control group at a total injected volume of 0.1 mL per rat.

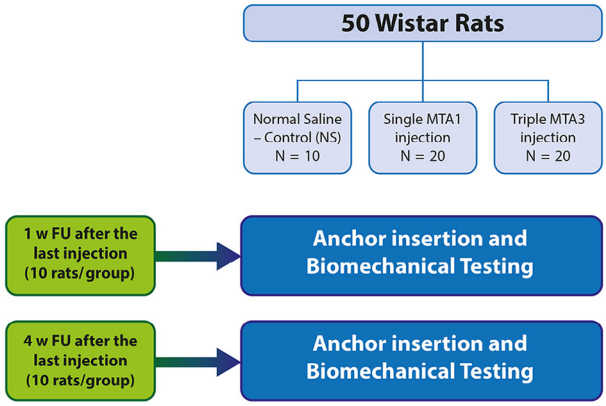

Figure 1 Study flowchart. FU, follow-up; MTA1, single methylprednisolone acetate injection; MTA3, triple methylprednisolone acetate injections.

All injections were performed under isoflurane-induced general anesthesia, as previously described.[10] In brief, the posterolateral corner of the acromion was identified using a 25-gauge needle rubbing the undersurface of the acromion and aiming anterolaterally into the subacromial space. The syringe plunger was inserted until no further resistance was felt during injection. The animals were returned to their cages after the injection. They were killed humanely by carbon dioxide inhalation as follows: 10 animals at 1 week after the final MTA injection and 10 animals at 4 weeks after the final MTA injection.

Biomechanical testing

A mini–suture anchor (orthodontic anchor screw; MIS Implants, Savyon, Israel), 1.6 mm in diameter, was inserted into the humeral head through the GT (Fig. 2). The anchor was inserted at a 45° angle in the direction of the medial humeral neck cortex. The distal part of the humerus was fixed onto a base in a vertical orientation. The anchor was loaded with a metal wire and fixed onto a clamp. The base and clamp were loaded into a biomaterials testing machine (model 4502; Instron, High Wycombe, UK) (Fig. 3). Specimens were pre-tensioned and subsequently pulled to failure (anchor pullout) at a rate of 0.1 mm/s. Maximal (failure) load was recorded for each specimen, and stiffness (slope) was calculated within the linear region of the load-displacement curve.

Statistical analysis

Before study initiation, a power analysis was performed regarding the primary outcome measure of maximal load to failure on biomechanical testing. The analysis was based on an earlier study that assessed RC tendon healing in rats after corticosteroid treatment.[10] Clinical significance was set at a 20% decrease in strength. With these evaluations for biomechanical testing, power of 80% was achieved using 10 animals per group with $\alpha = .05$. Power estimation was performed by the IBM SPSS SamplePower package (IBM, Armonk, NY, USA). Data are presented as mean ± standard deviation. The significance of differences between experimental groups was determined by the Student *t* test or by 1-way analysis

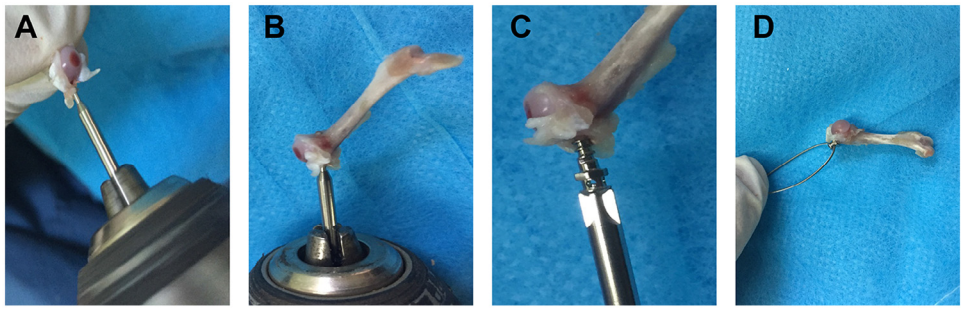

Figure 2 **(A, B)** A hole was made in the greater tuberosity with a high-speed drill. **(C, D)** A mini–suture anchor (orthodontic anchor screw; MIS Implants), 1.6 mm in diameter, was inserted into the humeral head through the greater tuberosity.

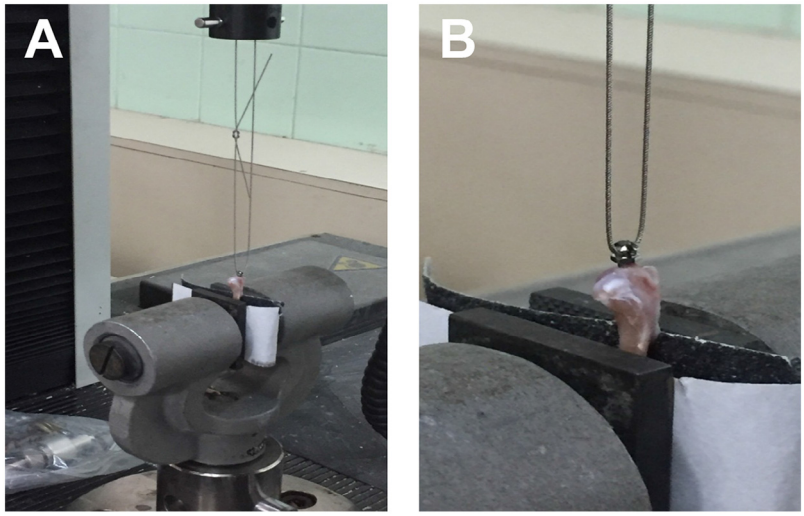

Figure 3 **(A)** The distal part of the humerus was fixed into a base. The anchor was loaded with a metal wire and fixed onto a clamp. **(B)** The base and clamp were loaded into a biomaterials testing machine.

of variance with the Tukey post hoc test (multiple groups). SPSS software (version 21; IBM) was used for data collection and analysis. Differences were considered statistically significant at $P < .05$.

Results

General observations

All the rats had normal gait patterns and food consumption postoperatively. There were no differences in weight between the treatment and control groups and no signs of local or systemic infection at any time point.

Suture anchor biomechanics at 1 week after last injection

A single MTA injection reduced the mean maximal pullout strength by 63.5% (10.3 ± 3.9 N) compared with a pullout strength of 28.2 ± 10 N in the control group ($P < .05$). Three MTA injections decreased the mean maximal pullout force by 56% (12.7 ± 5.2 N) compared with the control group ($P < .05$). There was no significant difference between the MTA1 and MTA3 groups ($P = .28$) (Fig. 4, *A*). Mean stiffness was 19 ± 9.1 N/mm in the control group compared with 5.78 ± 4.1 N/mm in the MTA1 group, representing a decrease of 69.6% ($P < .05$), and 8.2 ± 5.2 N/mm in the MTA3 group, representing a decrease of 56.8% ($P < .05$). There was no significant difference in stiffness between the MTA1 and MTA3 groups ($P = .305$) (Fig. 4, *B*).

Suture anchor biomechanics at 4 weeks after last injection

There was a significant increase in the mean maximal pullout strength at 4 weeks after the single and triple MTA injections versus the maximal pullout strength measured at 1 week (26.18 ± 10 N vs 10.3 ± 3.9 N and 21.19 ± 5.7 N vs 12.7 ± 5.2 N, respectively; $P < .05$) (Fig. 4, *A*). At 4 weeks, the mean maximal pullout strength was 26.18 ± 10 N after a single MTA injection and 21.19 ± 5.7 N after triple MTA injections, which were 92.8% and 80.9%, respectively, of the pullout strength

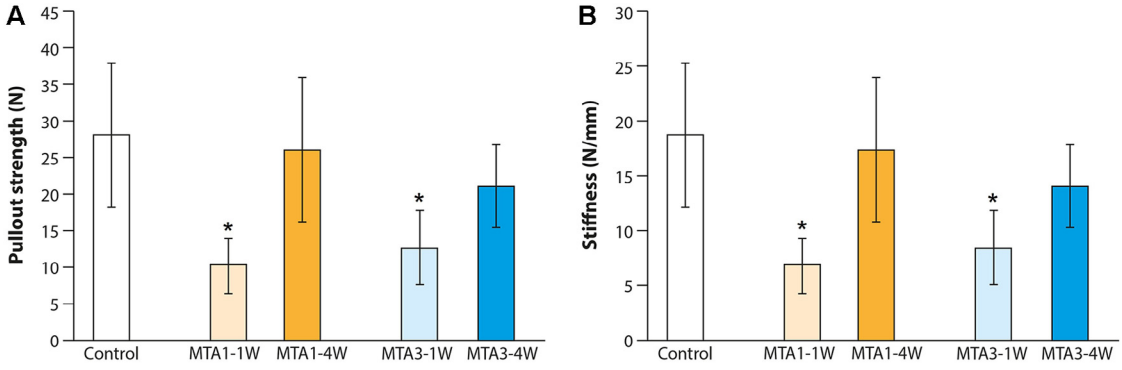

Figure 4 Biomechanical testing results. **(A)** Mean maximal pullout strength. **(B)** Mean stiffness. Data are reported as mean ± standard deviation. The *asterisks* indicate $P < .05$ versus control group by analysis of variance. MTA1, single methylprednisolone acetate injection; MTA3, triple methylprednisolone acetate injections; 1W, 1 week; 4W, 4 weeks.

measured in the control group (neither difference was statistically significant) (Fig. 4, *A*). In addition, a substantial increase in mean stiffness was measured at 4 weeks versus mean stiffness measured at 1 week in rats treated with single and triple injections (14.4 ± 7.79 N/mm vs 5.78 ± 4.1 N/mm and 15.9 ± 6.7 N/mm vs 8.2 ± 5.2 N/mm, respectively; $P < .05$) (Fig. 4, *B*). There was no statistically significant difference in stiffness between the 3 groups at 4 weeks.

Discussion

The principal finding of this study was that exposure of the rats' GT to either single or triple MTA injections significantly decreased the pullout strength of the suture anchor at 1 week after the final injection. The study hypothesis that corticosteroid injections deleteriously affected the pullout strength of suture anchors in rats was based on the recently published results of Maman et al,[10] who demonstrated deleterious effects of repeated MTA injections on GT bone quality in rats with undamaged RCs at 1 week after the last injection. Specifically, micro–computed tomographic analysis showed signs of osteopenia, such as significantly lower GT volume fraction, trabecular number, and connectivity density. It is important to note that our study revealed that pullout force and stiffness of the anchors were significantly improved at 4 weeks after the final MTA treatment. This finding indicates that MTA-induced osteopenia is apparently transient in nature.

When dealing with RC repair outcomes, it is important to take into consideration the sutures, anchor types,[14] quality of tendons, tear size, chronicity of the tear, and quality of the tuberosity bones. BMD plays an important role in the outcome; thus, a lower BMD will result in easier pullout of the anchors from the humerus.[16] Some studies have suggested that BMD may play a role in suture anchor failure.[7] There is also evidence suggesting that RC pathology may lead to a progression of proximal humeral osteoporosis in elderly patients.[7] Barber et al[1] tested biodegradable suture anchors in cadavers that had been divided into 2 age groups, with a mean age of 54 years in the younger group and 70 years in the older group. They found that anchors placed in the older cadaveric group failed (ie, could be pulled out) at significantly lower loads.

Tingart et al[16] evaluated total BMD in regions of the GT in a biomechanical cadaveric model using quantitative computed tomography scans. They demonstrated significant variations in total bone density of the GT, as well as significant differences in screw-type anchor pullout strength dependent on the density of the bone.[16] Anchor pullout strength was significantly higher in regions of the proximal humerus with a higher total BMD than in regions with a lower BMD.

The influence of oral corticosteroids on bone has been widely investigated. Glucocorticoid-induced osteoporosis is the most common cause of secondary osteoporosis in humans.[6] The skeletal effects of glucocorticoids include both direct and indirect actions on bone that can result in an early and transient increase in bone resorption accompanied by a decrease in bone formation, which persists for the duration of glucocorticoid therapy. Previous studies have shown that glucocorticoid administration resulted in sustained reductions in bone formation because of decreased osteoblast differentiation and activity and increased osteoblast and osteocyte apoptosis.[15] Rapid bone loss and increased fracture risk occur soon after the initiation of glucocorticoid therapy and are dose dependent.[3]

Data on the effects of locally administered glucocorticoids are very scarce. A study by Kim and Hwang[8] focused on the relationship between BMD and the frequent administration of epidural steroid injections in postmenopausal women with lower back pain and concluded that multiple epidural steroid injections could be responsible for the reduction of BMD in that population.

To date, there has been only 1 study available in the English-language literature on the local effects of subacromially injected steroids on GT.[10] Using micro–computed tomographic analysis, those investigators found significantly lower GT volume fraction, trabecular number, and connectivity density. The results of our study support the concept that there is both decreased pullout strength and decreased stiffness after MTA injections, at least in the initial rapid phase of glucocorticoid-induced

bone loss. However, the subsequent increase in both of these parameters suggests that discontinuation of steroid administration is followed by a reparative phase with high bone turnover. Further investigation is needed to validate these findings and to explore the mechanisms involved.

This study's limitations include those that are common to all controlled animal trials. Humans tend to present with intrinsic degenerative changes in the torn RC tendon (tendinosis), tendon retraction, and osteoporosis of the GT in the shoulder, which was not mimicked in the rat model. The loading of the anchor used in the study does not precisely mimic the load experienced after an RC repair. In addition, only male rats were included in this study, under the consideration that the reproductive cycles and hormone fluctuations in female animals could confound the results.

Conclusions

Within the limitations of this study, our results clearly show a significant detrimental effect of corticosteroid exposure on the pullout strength of suture anchors shortly after the administration of steroids. The potential detrimental effects of subacromial corticosteroid injections should be taken into account among patients who are candidates for RC repair. Because these effects are transient and may resolve within a relatively short period, it would appear to be prudent to have a waiting period between the last subacromial corticosteroid injection and RC repair surgery in which suture anchors are used. More studies, including animal and clinical trials, are needed to further investigate the effect of corticosteroid exposure on pullout strength to more precisely delineate the time frame of the transient osteoporosis.

Disclaimer

The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

References

1. Barber FA, Coons DA, Ruiz-Suarez M. Cyclic load testing of biodegradable suture anchors containing 2 high-strength sutures. Arthroscopy 2007;23:355-60. http://dx.doi.org/10.1016/j.arthro.2006.12.009
2. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int 2007;18:1319-28. http://dx.doi.org/10.1007/s00198-007-0394-0
3. Compston J. Management of glucocorticoid-induced osteoporosis. Nat Rev Rheumatol 2010;6:82-8. http://dx.doi.org/10.1038/nrrheum.2009.259
4. Cummins CA, Murrell GA. Mode of failure for rotator cuff repair with suture anchors identified at revision surgery. J Shoulder Elbow Surg 2003;12:128-33. http://dx.doi.org/10.1067/mse.2003.21
5. Fermont AJ, Wolterbeek N, Wessel RN, Baeyens JP, de Bie RA. Prognostic factors for successful recovery after arthroscopic rotator cuff repair: a systematic literature review. J Orthop Sports Phys Ther 2014;44:153-63. http://dx.doi.org/10.2519/jospt.2014.4832
6. Guañabens N, Gifre L, Peris P. The role of Wnt signaling and sclerostin in the pathogenesis of glucocorticoid-induced osteoporosis. Curr Osteoporos Rep 2014;12:90-7. http://dx.doi.org/10.1007/s11914-014-0197-0
7. Kannus P, Leppala J, Lehto M, Sievanen H, Heinonen A, Jarvinen M. A rotator cuff rupture produces permanent osteoporosis in the affected extremity, but not in those with whom shoulder function has returned to normal. J Bone Miner Res 1995;10:1263-71.
8. Kim S, Hwang B. Relationship between bone mineral density and the frequent administration of epidural steroid injections in postmenopausal women with low back pain. Pain Res Manag 2014;19:30-4. http://dx.doi.org/10.1155/2014/870145
9. Ma R, Chow R, Choi L, Diduch D. Arthroscopic rotator cuff repair: suture anchor properties, modes of failure and technical considerations. Expert Rev Med Devices 2011;8:377-87. http://dx.doi.org/10.1586/erd.11.4
10. Maman E, Yehuda C, Pritsch T, Morag G, Brosh T, Sharfman Z, et al. Detrimental effect of repeated and single subacromial corticosteroid injections on the intact and injured rotator cuff: a biomechanical and imaging study in rats. Am J Sports Med 2016;44:177-82. http://dx.doi.org/10.1177/0363546515591266
11. Meyer DC, Nyffeler RW, Fucentese SF, Gerber C. Failure of suture material at suture anchor eyelets. Arthroscopy 2002;18:1013-9. http://dx.doi.org/10.1053/jars.2002.36115
12. Mikolyzk DK, Wei AS, Tonino P, Marra G, Williams DA, Himes RD, et al. Effect of corticosteroids on the biomechanical strength of rat rotator cuff tendon. J Bone Joint Surg Am 2009;91:1172-80. http://dx.doi.org/10.2106/JBJS.H.00191
13. Milgrom C, Schaffler M, Gilbert S, van Holsbeeck M. Rotator-cuff changes in asymptomatic adults. The effect of age, hand dominance and gender. J Bone Joint Surg Br 1995;77:296-8.
14. Nagra NS, Zargar N, Smith RD, Carr AJ. Mechanical properties of all-suture anchors for rotator cuff repair. Bone Joint Res 2017;6:82-9. http://dx.doi.org/10.1302/2046-3758.62.BJR-2016-0225.R1
15. O'Brien CA, Jia D, Plotkin LI, Bellido T, Powers CC, Stewart SA, et al. Glucocorticoids act directly on osteoblasts and osteocytes to induce their apoptosis and reduce bone formation and strength. Endocrinology 2004;145:1835-41. http://dx.doi.org/10.1210/en.2003-0990
16. Tingart MJ, Apreleva M, Lehtinen J, Zurakowski D, Warner JJ. Anchor design and bone mineral density affect the pull-out strength of suture anchors in rotator cuff repair: which anchors are best to use in patients with low bone quality? Am J Sports Med 2004;32:1466-73. http://dx.doi.org/10.1177/0363546503262644
17. Yamaguchi K, Ditsios K, Middleton WD, Hildebolt CF, Galatz LM, Teefey SA. The demographic and morphological features of rotator cuff disease. A comparison of asymptomatic and symptomatic shoulders. J Bone Joint Surg Am 2006;88:1699-704. http://dx.doi.org/10.2106/JBJS.E.00835