J Shoulder Elbow Surg (2019) 28, 164–169

ELSEVIER

Journal of Shoulder and Elbow Surgery

www.elsevier.com/locate/ymse

Safety evaluation of a laxity-minimizing suture at 5 days and 6 weeks after repair of a sheep infraspinatus tendon

Paul J. Favorito, MD[a,*], David B. Spenciner, PE, ScM, FASM[b,c], Timothy R. Muench, DVM, MS, PhD[d], Jolee Bartrom, BS, RLAT[e], Richard K. Ryu, MD[f]

[a]*Wellington Orthopedic & Sports Medicine, Cincinnati, OH, USA*
[b]*DePuy Synthes Mitek Sports Medicine, Raynham, MA, USA*
[c]*Department of Biomedical Engineering, Rensselaer Polytechnic Institute, Troy, NY, USA*
[d]*Medical Device Business Services, Somerville, NJ, USA*
[e]*North American Science Associates Inc. (NAMSA), Northwood, OH, USA*
[f]*Ryu Hurvitz Orthopedic Clinic, Santa Barbara, CA, USA*

Background: The ideal rotator cuff repair achieves high initial fixation strength and secure tendon-to-bone apposition until biological healing occurs. A suture that reacts to the local stress environment by minimizing suture laxity across the repair could theoretically maintain soft-tissue apposition to bone and therefore improve healing.

Methods: By use of an in vivo ovine shoulder model, the infraspinatus tendon was transected and then repaired with either a laxity-minimizing suture or a traditional high tensile suture. The purpose of this study was to evaluate both sutures' safety at 5 days and 6 weeks after repair.

Results: The macroscopic and microscopic analyses of the repair sites showed similar amounts of surgical trauma. There was no evidence of cheese wiring or tissue necrosis of the repaired tendons for either suture. There was no evidence of systematic toxicity in any animal. The maximum gap between cut edges of the tendon for repairs with the predicate suture was approximately twice the gap for the laxity-minimizing suture.

Conclusion: The laxity-minimizing suture was as safe at 5 days and 6 weeks as the predicate suture. Neither suture contributed to local tissue damage or particle generation leading to adverse systematic consequences. An additional observation was that the maximum gap between cut edges of the tendon for repairs with the predicate suture was approximately twice the gap for the laxity-minimizing suture.

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

Keywords: In vivo; safety study; suture; laxity minimizing; ovine; rotator cuff; Good Laboratory Practice (GLP)

The Institutional Animal Care and Use Committee board at North American Science Associates Inc. (NAMSA) approved this Good Laboratory Practice animal study (No. 17T-46632).

*Reprint requests: Paul J. Favorito, MD, Wellington Orthopaedic & Sports Medicine, 7575 Five Mile Road, Cincinnati, OH 45230, USA.

E-mail address: favbone@aol.com (P.J. Favorito).

Rotator cuff tears occur frequently and may be a source of disability for patients.[16] When operative treatment is chosen, multiple studies have demonstrated improved patient outcomes following rotator cuff repair.[7,21] Studies have shown

1058-2746/$ - see front matter © 2018 Journal of Shoulder and Elbow Surgery Board of Trustees. All rights reserved.
https://doi.org/10.1016/j.jse.2018.05.043

that following repair, patients have better results if the tendon heals.[9,13] The ideal rotator cuff repair achieves high initial fixation strength and secure tendon-to-bone apposition until biological healing occurs.[14] Many factors, including the choice of suture, contribute to a successful outcome.[8]

Multiple fixation techniques and constructs, including the use of suture anchors or transosseous bone tunnels, may be used for rotator cuff repair. In the early stage of tendon healing, the formation of vessels followed by extracellular matrix production contributes to the initial scar to secure the tendon.[20] During the initial healing period, it is important to achieve secure tendon-to-bone fixation. If any portion of the fixation construct fails to maintain satisfactory suture tension (eg, anchor migration, suture elongation, or cheese wiring through bone), healing may be compromised and structural failure may occur.[1] Although most repairs today are performed with high-strength, abrasion-resistant sutures, some sutures have a tendency to slip and initial tension is lost.[3]

The ideal rotator cuff repair construct must optimize suture-to-bone fixation, suture-to-tendon fixation, tendon-to-bone contact pressure, abrasion resistance of suture, suture strength, knot security, loop security, and restoration of the anatomic rotator cuff footprint.[2,5] Brassart et al[4] demonstrated that after repair, the contact force between the tendon and bone decreases over the first few minutes following completion of the knot tying. In addition and to minimize postoperative stiffness by allowing glenohumeral motion, the suture tension imparted at time 0 may not be maintained in the early postoperative period.[11] Consequently, a suture that reacts to the local stress environment by minimizing suture laxity across the repair could theoretically maintain bony apposition of the soft tissue and therefore improve healing. However, too robust of a suture response could potentially over-tighten the soft tissue, restrict blood flow, and create ischemia.[10,12] Presently, there are no commercially available sutures that have a laxity-minimizing effect.

By use of an ovine infraspinatus tendon model, the purpose of this study was to evaluate a laxity-minimizing suture for both local soft-tissue damage and systemic effects at 5 days and 6 weeks after surgery. The hypothesis was that this suture would have a similar safety profile to a traditional suture.

Materials and methods

A total of 22 Dorset/cross sheep (including 2 animals assigned to serve as replacement animals) weighing 50-79 kg were obtained for this study, which was conducted at an independent testing laboratory (NAMSA). This study was performed in compliance with Food and Drug Administration Good Laboratory Practice regulations. At 5 days and 6 weeks after surgery, macroscopic and microscopic assessments of the tendon repair site and selected organs and tissues were performed.

All animals were quarantined and underwent standard veterinary examinations to confirm their health status prior to study assignment. One animal was rejected as it favored its right forelimb throughout the acclimation period. This left a total of 21 sheep, all of which underwent partial, midsubstance transection of the right infraspinatus tendon and subsequent suture repair. Animals were arbitrarily assigned to the test suture or predicate suture group and arbitrarily assigned to a surgery day. All 4 groups had 5 animals, except for the 6-week test suture group, which had 6 animals.

Two types of free sutures on needles were used to make the repairs in this study. The test suture, Dynacord (DePuy Synthes Mitek Sports Medicine, Raynham, MA, USA), is a suture that has been designed to minimize suture laxity during the healing period. If a minimum amount of tension is not applied to the suture, an inner core of 12% salt-impregnated silicone expands radially and the suture shortens in length until tension is restored. The predicate suture was a traditional suture: FiberWire (Arthrex, Naples, FL, USA). Except for being oversized in diameter, both sutures meet the *United States Pharmacopeia* requirements for No. 2 suture. Both the test and predicate sutures comprise inner and outer sheaths manufactured primarily from fibers of ultrahigh-molecular-weight polyethylene and polyester poly(ethylene terephthalate). The test suture has a silicone and salt composite core, while the predicate suture has silicone added to the outer surface of the suture to improve the handling and knot-tying characteristics.[15]

Prior to each surgical procedure, the surgeon used a custom, load cell–based training device, with the goal of reaching a 40-N approximation force while tying the initial 2 throws of a square knot. It has been estimated previously that the remnant tensile load on spanning sutures following a double-row rotator cuff repair is 20 N[18]; therefore a 40-N force represents twice this force (thus ensuring knot security throughout the study).

Surgical procedure and postoperative care

The animals fasted prior to the implantation surgical procedure, and accepted veterinary care standards were followed. The incision sites were aseptically prepared and draped for the procedure. The right infraspinatus tendon was exposed through a lateral curved incision over the shoulder joint. The tendon was marked with a surgical marker approximately at the midway point between the attachment to the tuberosity and the musculotendinous junction. The length of the marking was approximately 10-12 mm and comprised only the caudal half (50% ± 10%) of the tendon width at that location. Using the designated suture for the animal, the area around the marking was stitched using 2 parallel series of locking suture patterns (ie, Krackow stitches; Fig. 1). Each series included 3 locking sutures, and the spacing between suture passes was approximately 5 mm. The suture was tensioned between passes through the tissue. A narrow malleable retractor with smooth edges was used to protect the deep tissues from the needle. The locking sutures were placed in the dorsal and ventral tendon regions in such a manner that the suture tails (to be tied from each series) protruded from each side of the marked tendon. Then, the tendon was transected along the prior marking. All slack was removed from the suture loops by pulling on the free limbs, and the sutures were tied with a square knot to approximate a 40-N force. The gap between the 2 ends of the tendon (if present) was measured in 3 places (where the transection began, at the middle of the transection, and at the caudal edge of the transection) using a ruler. Then, the fascia and skin were closed in typical fashion.

Prior to recovery from the anesthetic, each animal was placed in a suspension system to which the animals had already been acclimated (Medium Sling; Munks Livestock Sling MFG, Anacortes, WA, USA). Each animal was slightly elevated above the ground or

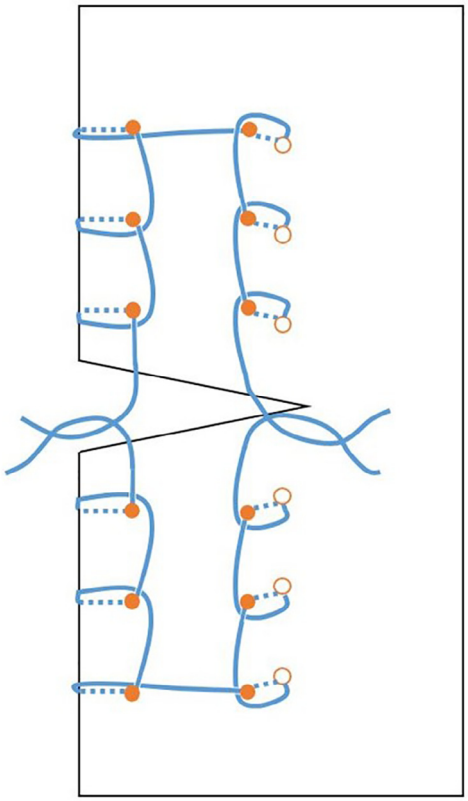

Figure 1 Pattern of tendon repair showing midsubstance partial transection and 2 sets of locking Krackow stitches (*solid lines* show suture superficial to tendon while *dotted lines* show suture deep to tendon).

could toe touch but was unable to bear full body weight until term or 2 weeks postoperatively, whichever occurred first. All animals were monitored for symptoms of pain, distress, and physical abnormalities to ensure that the suspension system placement was appropriate and were gradually off-loaded to transition back to full weight bearing.

Postoperative evaluation

Depending on the study group, animals were brought to term either 5 days or 6 weeks after the implantation procedures. Each animal was euthanized by intravenous injection of a pentobarbital sodium–based euthanasia solution in accordance with accepted American Veterinary Medical Association guidelines.

Immediately after euthanasia, a veterinary pathologist (T.R.M.) performed a full necropsy with macroscopic evaluation of the following organs and tissues: repaired tendon, skin, hair, eyes, muscles, lymph nodes (mesenteric, thoracic, and axillary), peritoneum, stomach, large and small intestine, brain, femoral bone marrow, digestive tract, heart, pericardium, lungs, liver, adrenals, spleen, pancreas, urinary bladder, kidney, lacrimal gland, pituitary, salivary gland, sciatic nerve, spinal cord, reproductive organs, diaphragm, and trachea. Macroscopic changes to the repair site were scored on a 4-point scale, while evidence of surgical trauma was scored on a 5-point scale. In addition to harvesting of the tendon at the repair site, tissue sections

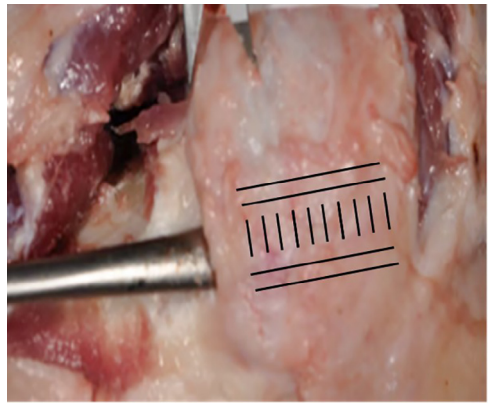

Figure 2 Schema of tissue slices used for histologic evaluation of repaired tendons showing 2 transverse slices proximal to partial transection, 2 transverse slices distal to partial transection, and 10 axial slices along line of transection.

were taken from the contralateral infraspinatus tendon, as well as muscle from the contralateral shoulder and ipsilateral thigh; mesenteric, thoracic, and axillary lymph nodes; heart; liver; adrenals; spleen; pancreas; kidney; and ovaries. For all animals, any additional abnormal organs and/or tissues were documented, macroscopically evaluated, and harvested for tissue sections.

All collected tissues were placed in 10% neutral buffered formalin and then processed by embedding in paraffin, sectioning, and staining for microscopic evaluation. Each 5- to 7-µm section was prepared with 2 slides: 1 stained with hematoxylin-eosin and the other stained with picrosirius red. For the repaired tendon, a schema (Fig. 2) was prepared to ensure that appropriate areas of the tendon would be examined to thoroughly evaluate the interface between the soft tissue and suture. The presence of foreign debris was scored on a 3-point scale, while degenerative or reparative alterations, healing between cut edges of the tendons, and overall healing were score on 5-point scales. The maximum gap between cut edges of the tendon was measured on the histology slides, and a t test was performed to compare the gap width between suture groups at both time points. The significance level was set to .05 a priori, and equal variances were assumed.

Results

All operations were performed as described, and the intended repair was completed. All animals tolerated the surgical procedures well. There were no complications associated with the tendon repair for any animal, although several animals in the 5-day group had subcutaneous tissue edema around the suspension system straps. In addition, in both the test and predicate groups, the necropsy findings revealed incidental spontaneous background lesions that are commonly encountered in adult sheep (ie, small to moderately sized thick-walled abscesses that contained caseous material). These lesions, which were mineralizing in many cases, were chronic in nature and were likely present in the animals prior to commencement of the study and unrelated to the tendon repair. Six animals had minor adhesions involving the lungs, thoracic wall, mediastinum, diaphragm, liver, and gastrointestinal

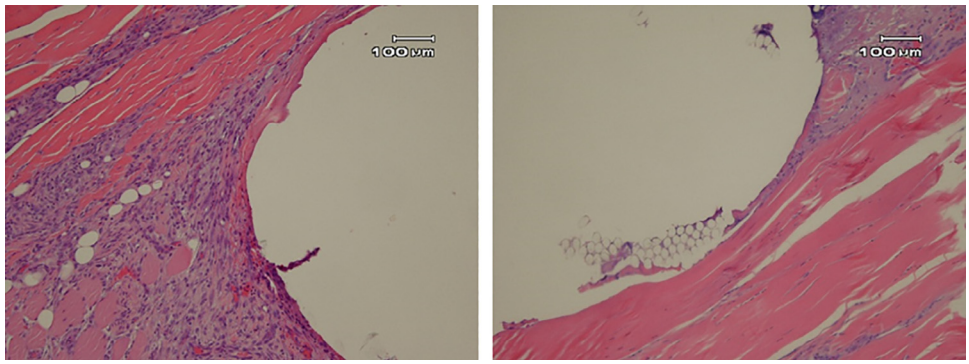

Figure 3 Representative histologic sections (hematoxylin-eosin staining) from 5-day animals for test suture (*left*) and control suture (*right*). In both images, surgical trauma was the predominant tissue change and there was no evidence of necrosis.

tract. All adhesions appeared to be chronic and unrelated to the surgical intervention. At necropsy, there were no macroscopic alterations observed in the following anatomic locations: eye, mesenteric and thoracic lymph nodes, abdominal cavity (peritoneum), rumen, omasum, reticulum, brain (including pituitary gland), femur (muscle, cortical bone, and medullary cavity), pancreas, adrenal glands, spleen, urinary bladder, lacrimal glands, salivary glands, sciatic nerve, spinal cord, ovaries and remaining reproductive tract, and contralateral infraspinatus tendon and muscle. Microscopically, there were scattered incidences of sarcocysts and infrequent areas of the liver, heart, and muscles consistent with inflammation, but these did not demonstrate a treatment-related trend. One animal had chronic mastitis (noted prior to study inception and confirmed microscopically).

Five-day analysis

The macroscopic and microscopic analyses of the repair sites showed similar amounts of surgical trauma between groups. Consistent with early healing, fibrin clots were identified at the margins of the tendon cut edges. There was no evidence of cheese wiring or tissue necrosis of any repaired tendons (Fig. 3). Similarly, organ and tissue evaluation revealed no evidence of systematic toxicity in any animal.

Six-week analysis

There was no evidence of suture degradation for either group. All repair sites had fibrous tissue infiltration without cheese wiring or necrosis. Two repairs with predicate sutures had both macroscopic and microscopic evidence of gap formation at the repair site. There were no particles generated in association with either the test or predicate suture either at the repair site or in the lymph nodes, and there was no degradation of any sutures. Organ and tissue evaluation revealed no evidence of systematic toxicity in any animal.

In general, the maximum gap between cut edges of the tendon for repairs with the predicate suture was approximately twice the gap for the test suture (Fig. 4). The difference in average maximum gap approached, but did not reach, statistical significance at 5 days ($P = .053$) and was statistically significant at 6 weeks ($P = .002$).

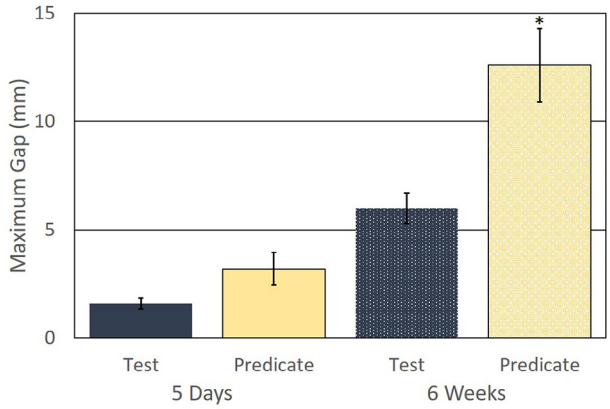

Figure 4 Average maximum gap (in millimeters) with standard deviation (*error bars*) at 5 days (*solid bars*) and 6 weeks (*dotted bars*) for test (*dark bars*) and predicate (*light bars*) suture repair groups. There was a statistically significant difference between the mean values at 6 weeks ($P = .002$, *asterisk*) but not at 5 days ($P = .053$).

Discussion

Two components of suture safety—over-tightening leading to tendon necrosis and suture particle development and migration—were evaluated. The study proved the hypothesis that in an in vivo ovine rotator cuff repair model, the laxity-minimizing suture would have a similar safety profile to the predicate suture. Neither suture contributed to local tissue damage or adverse systematic consequences at 5 days or 6 weeks. In addition, it was observed that the maximum gap between cut edges of the tendon for repairs with the predicate suture was approximately twice the gap for the laxity-minimizing suture.

The laxity-minimizing suture has an inner core of salt-impregnated silicone. When exposed to the local in vivo environment, the silicone core could theoretically degrade and lead to particulate debris. Although silicone has been incorporated into commonly used orthopedic sutures,[6] there are few reports of clinical complications attributed to its presence. Mack et al[15] reported 5 cases in which the suture was implicated in draining sinuses following lower extremity amputations in military personnel. Ollivere et al[17] and Warme et al[19] reported similar findings in Achilles tendon repairs and open capsular shift in the shoulder, respectively. Only Mack et al identified the presence of silicone-containing granulomas and specifically attributed 1 patient's complications to the presence of silicone in the sutures. In our study, the absence of silicone-related inflammation or a foreign-body reaction for either silicone-containing suture is encouraging.

Kim et al[11] evaluated suture knots following labral repair. They confirmed that knots migrate with motion and that both shoulder motion and loosening of half-hitches are important contributing factors. A laxity-minimizing suture has the potential benefits of maintaining satisfactory suture tension and knot security tension because, as the suture is exposed to body fluid, salt elutes out of the core and fluid hydrates the core, driving the suture to expand radially and contract axially. However, this process carries the possibility of overtensioning the soft tissue. Evaluation of rotator cuff repair in a rabbit model confirmed that overcompression of tendons reduces local tissue perfusion.[10] While tissue perfusion was not measured in our study, there was no evidence of tissue necrosis, suggesting that neither suture overcompressed the tendons.

Although not the purpose of the study, it was observed that the maximum gap between cut edges of the tendon for repairs with the predicate suture was approximately twice the gap for the laxity-minimizing suture. This may be the first report of in vivo tendon gap reduction specifically attributable to a laxity-minimizing suture.

The most obvious limitations in this study are that the ovine response and human response to suture may differ, each test group had a small number of subjects, and necropsies were performed at only 2 points in time. The host response was evaluated at 6 weeks, but additional differences may occur in a later time period. Further investigations may be beneficial to determine both the clinical applications and any longer-term adverse consequences related to the suture. Despite preoperative knot-tying training, it is likely that there were some inconsistencies in final knot tension. In addition, the concentration of salt in the test suture was purposefully higher than that in the intended suture product. This allowed evaluation of a worst-case scenario with regard to potential local and systemic tissue effects but may have led to an overstatement of the gap reduction effect. Additional testing would allow for a more accurate determination of the laxity-minimizing properties of the commercialized suture with a salt concentration of less than 12%.

Conclusion

The laxity-minimizing suture was as safe at 5 days and 6 weeks as the predicate suture. Neither suture contributed to local tissue damage or particle generation leading to adverse systematic consequences. An additional observation was that the maximum gap between cut edges of the tendon for repairs with the predicate suture was approximately twice the gap for the laxity-minimizing suture.

Disclaimer

This study was funded by Johnson & Johnson. David B. Spenciner is an employee of Johnson & Johnson. Timothy R. Muench is an employee of Johnson & Johnson. Jolee Bartrom is an employee of the animal facility study site (North American Science Associates Inc. [NAMSA]). Richard K. Ryu was compensated as a consultant for his involvement.

The other author, his immediate family, and any research foundations with which he is affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

References

1. Abtahi AM, Granger EK, Tashjian RZ. Factors affecting healing after arthroscopic rotator cuff repair. World J Orthop 2015;6:211-20. http://dx.doi.org/10.5312/wjo.v6.i2.211
2. Andres BM, Lam PH, Murrell GA. Tension, abduction, and surgical technique affect footprint compression after rotator cuff repair in an ovine model. J Shoulder Elbow Surg 2010;19:1018-27. http://dx.doi.org/10.1016/j.jse.2010.04.005
3. Barber FA, Herbert MA, Beavis RC. Cyclic load and failure behavior of arthroscopic knots and high strength sutures. Arthroscopy 2009;25:192-9. http://dx.doi.org/10.1016/j.arthro.2008.09.010
4. Brassart N, Sanghavi S, Hansen UN, Emery RJ, Amis AA. Loss of rotator cuff tendon-to-bone interface pressure after reattachment using a suture anchor. J Shoulder Elbow Surg 2008;17:784-9. http://dx.doi.org/10.1016/j.jse.2008.01.140
5. Burkhart SS, Lo IK. Arthroscopic rotator cuff repair. J Am Acad Orthop Surg 2006;14:333-46.
6. Carr BJ, Ochoa L, Rankin D, Owens BD. Biologic response to orthopedic sutures: a histologic study in a rabbit model. Orthopedics 2009;32:828. http://dx.doi.org/10.3928/01477447-20090922-11
7. Galatz LM, Griggs S, Cameron BD, Ianotti JP. Prospective longitudinal analysis of postoperative shoulder function : a ten-year follow-up study of full-thickness rotator cuff tears. J Bone Joint Surg Am 2001;83:1052-6.
8. Gerber C, Schneeberger AG, Perren SM, Nyffeler RW. Experimental rotator cuff repair. A preliminary study. J Bone Joint Surg Am 1999;81:1281-90.
9. Harryman DT II, Mack LA, Wang KY, Jackins SE, Richardson ML, Matsen FA III. Repairs of the rotator cuff. Correlation of functional results with integrity of the cuff. J Bone Joint Surg Am 1991;73:982-9.

10. Kim SH, Cho WS, Joung HY, Choi YE, Jung M. Perfusion of the rotator cuff tendon according to the repair configuration using an indocyanine green fluorescence arthroscope: a preliminary report. Am J Sports Med 2016;45:659-65. http://dx.doi.org/10.1177/0363546516669778
11. Kim SH, Crater RB, Hargens AR. Movement-induced knot migration after anterior stabilization in the shoulder. Arthroscopy 2013;29:485-90. http://dx.doi.org/10.1016/j.arthro.2012.10.011
12. Kim SH, Kim J, Choi YE, Lee HW. Healing disturbance with suture bridge configuration repair in rabbit rotator cuff tear. J Shoulder Elbow Surg 2016;25:478-86. http://dx.doi.org/10.1016/j.jse.2015.08.035
13. Liem D, Lichtenberg S, Magosch P, Habermeyer P. Magnetic resonance imaging of arthroscopic supraspinatus tendon repair. J Bone Joint Surg Am 2007;89:1770-6. http://dx.doi.org/10.2106/JBJS.F.00749
14. Lorbach O, Baums MH, Kostuj T, Pauly S, Scheibel M, Carr A, et al. Advances in biology and mechanics of rotator cuff repair. Knee Surg Sports Traumatol Arthrosc 2015;23:530-41. http://dx.doi.org/10.1007/s00167-014-3487-2
15. Mack AW, Freedman BA, Shawen SB, Gajewski DA, Kalasinsky VF, Lewin-Smith MR. Wound complications following the use of FiberWire in lower-extremity traumatic amputations. A case series. J Bone Joint Surg Am 2009;91:680-5. http://dx.doi.org/10.2106/JBJS.H.00110
16. Mather RC III, Koenig L, Acevedo D, Dall TM, Gallo P, Romeo A, et al. The societal and economic value of rotator cuff repair. J Bone Joint Surg Am 2013;95:1993-2000. http://dx.doi.org/10.2106/JBJS.L.01495
17. Ollivere BJ, Bosman HA, Bearcroft PW, Robinson AHN. Foreign body granulomatous reaction associated with polyethelene "Fiberwire((R))" suture material used in Achilles tendon repair. Foot Ankle Surg 2014;20:e27-9. http://dx.doi.org/10.1016/j.fas.2014.01.006
18. Sano H, Tokunaga M, Noguchi M, Inawashiro T, Irie T, Abe H, et al. Tight medial knot tying may increase retearing risk after transosseous equivalent repair of rotator cuff tendon. Biomed Mater Eng 2017;28:267-77. http://dx.doi.org/10.3233/BME-171673
19. Warme WJ, Burroughs RF, Ferguson T. Late foreign-body reaction to Ticron sutures following inferior capsular shift: a case report. Am J Sports Med 2004;32:232-6. http://dx.doi.org/10.1177/0363546503260728
20. Wildemann B, Klatte F. Biological aspects of rotator cuff healing. Muscles Ligaments Tendons J 2011;1:161-8.
21. Zandi H, Coghlan JA, Bell SN. Mini-incision rotator cuff repair: a longitudinal assessment with no deterioration of result up to nine years. J Shoulder Elbow Surg 2006;15:135-9. http://dx.doi.org/10.1016/j.jse.2005.06.008