Tendon Collagen Crosslinking Offers Potential to Improve Suture Pullout in Rotator Cuff Repair: An Ex Vivo Sheep Study

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Abstract

Background The suture-tendon interface is often the weakest link in tendon to bone repair of massive rotator cuff tears. Genipin is a low-toxicity collagen crosslinker derived from the gardenia fruit that has been shown to augment collagen tissue strength and mechanically arrest tendon-tear progression.

Question/Purpose The purpose of the current study was to evaluate whether genipin crosslinking can sufficiently augment the suture-tendon interface to improve suture pullout strength using simple single-loop sutures and the modified Mason-Allen technique. The study also aimed to

assess whether time of genipin treatment is a relevant factor in efficacy.

Methods In an ex vivo (cadaveric) sheep rotator cuff tendon model, a total of 142 suture pullout tests were performed on 32 infraspinatus tendons. Each tendon was prepared with three single-loop stitches. Two groups were pretreated by incubation in genipin solution for either 4 hours or 24 hours. Two corresponding control groups were incubated in phosphate buffered saline for the same periods. The same test protocol was applied to tendons using modified Mason-Allen technique stitch patterns. Each suture was loaded to failure on a universal materials testing machine. Suture pullout force, stiffness, and work to failure were calculated from force-displacement data, and then compared among the groups.

Results Median single-loop pullout force on tendons incubated for 24 hours in genipin yielded an approximately 30% increase in maximum pullout force for single-loop stitches with a median of 73 N (range, 56–114 N) compared with 56 N (range, 40–69 N; difference of medians = 17 N; $p = 0.028$), with corresponding increases in the required work to failure but not stiffness. Genipin treatment for 4 hours showed no added benefit for suture-pullout behavior (46 N, [range, 35–95 N] versus 45 N, [range, 28–63 N]; difference of medians, 1 N; $p = 1$). No tested genipin crosslinking conditions indicated benefit for tendons grasped using the modified Mason-Allen technique after 4 hours (162 N, [range, 143–193 N] versus 140 N, [range, 129–151 N]; difference of medians, 22 N; $p = 0.114$) or after 24 hours of crosslinking (172 N, [range, 42–183 N] versus 164 N [range, 151–180 N]; difference of medians, 8 N; $p = 0.886$).

Conclusion Exogenous collagen crosslinking in genipin can markedly improve resistance to pullout at the tendon-suture interface for simple stitch patterns while the modified Mason-Allen stitch showed no benefit in an ex vivo animal model.

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Clinical Relevance Tendon strength augmentation by genipin pretreatment offers the potential to improve suture retention properties. Future studies are warranted for the development of clinically viable intraoperative delivery strategies and in vivo testing for safety and efficacy.

Introduction

Rotator cuff tendon tear is a common cause of pain and disability with increasing prevalence with advanced age [13, 30]. Massive tears usually are chronic and associated with myotendinous retraction [25], loss of musculotendinous elasticity [22], muscle atrophy, and fatty infiltration of the muscle [21]. If a massive rotator cuff tear can be repaired, short- and long-term clinical results are excellent and joint degeneration can be markedly decelerated or even arrested [1, 6, 10, 18]. Tendon to bone anchorage strength, especially the suture-tendon interface, often is identified as the critical limit to successful rotator cuff repair [4, 11]. Many approaches have been attempted to improve the biomechanics of initial surgical repair, including optimized tendon grasping techniques [3, 19, 23], and strategic stitch positioning in the tendon [33]. Today, most rotator cuff repairs are performed arthroscopically. In contrast to open tendon repairs that allow technically demanding but mechanically robust suture patterns, arthroscopically implemented simple single-loop or mattress suturing techniques (in a single or double row) are most widely used. Because arthroscopic sutures may be biomechanically inferior, mechanical tissue augmentation has been introduced as one option to reinforce tendon repair. For instance incorporation of a superimposed human dermal allograft (eg, GRAFTJACKET[®]; Wright Medical Technology Inc, Memphis, TN, USA) has been reported to increase repair strength [5], but at additional cost and increased operation times [8].

Exogenous collagen crosslinking agents have emerged as a viable method to achieve tendon tissue augmentation, with therapeutic potential having been shown for certain clinical indications using experimental models and even human clinical application [17]. Among potential crosslinking agents, genipin is a naturally occurring crosslinker derived from the gardenia fruit that is used in traditional Chinese medicine, with little apparent toxicity [14]. Specifically in the tendon, genipin crosslinking can mechanically augment tendon biomechanical properties across a wide range of loading conditions: increasing tissue stiffness and failure stress, and dramatically slowing tendon-tear propagation under (in vitro) cyclic mechanical loading secondary to a biopsy punched lesion [15]. However, to our knowledge, no studies have evaluated genipin

in the laboratory to determine whether it might be harnessed to augment local tendon tissue properties to improve surgical handling. In this study, we sought to assess whether genipin crosslinking may be able to improve suture retention by inhibiting failure at the tendon-suture interface.

We therefore evaluated the hypothesis that genipin crosslinking can improve suture pullout strength, using simple sutures and the stronger suture configuration of the modified Mason-Allen technique. We also tested whether the time of genipin exposure is an important factor to achieve measurable mechanical effects. For these experiments we used an ex vivo sheep infraspinatus model, and investigated suture pullout in untreated (incubated in buffer only) and genipin crosslinked tendons. We hypothesized that genipin crosslinked tendons would have higher suture pullout forces for both suture types after a minimum of 4 hours incubation time in a high-concentration genipin crosslinking solution.

Materials and Methods

A total of 32 adult sheep shoulder specimens were obtained from a local abattoir. Although all animals were qualitatively uniform in size and tendon tissue quality, the sex and precise age of the animals were undocumented. All specimens were randomly allocated to the various test groups in an attempt to avoid selection bias. The infraspinatus tendon was sharply detached from its insertion site on the greater tuberosity and any remaining soft tissue was resected [15]. Freshly harvested tendons were wrapped in gauze moistened with phosphate buffered saline (PBS) solution and stored at -20°C until mechanical testing by established methods [4]. Before testing, the specimens were thawed overnight at 4°C and three sutures (one centered and two on either side), using a Number 2 high-strength braided polyethylene thread (USP Number 2 FiberWire[®]; Arthrex Inc, Naples, FL, USA), were set in a row 10 mm medial to the free lateral tendon margin (Fig. 1A). A suture loop was tied with two sliding half hitches followed by alternating half hitches for a total of seven throws [27]. Testing group sizes of eight and the genipin treatment concentration were selected based on power analysis of a previous comprehensive dose-response study on tendon explants [14]. Genipin crosslinked tendons ($n = 16$) were separated into two groups incubated at 36°C for 4 hours ($n = 8$) or 24 hours ($n = 8$) in 20 mmol/L genipin (Challenge Bioproducts Co, Ltd, Taiwan, Republic of China) in 1 mmol/L dimethyl sulfoxide (Sigma-Aldrich, St Louis, MO, USA) and PBS. Control group tendons ($n = 16$) were incubated in PBS for the same period. After treatment, all samples were

Fig. 1A–C The experimental setup used to measure the tendon-suture pullout force is shown. **(A)** Three single-loop sutures were performed in a control group of sheep infraspinatus tendons. **(B)** Three modified Mason-Allen sutures were performed in a genipin-

treated tendon in the position where the first set of single-loop stitches cut through the tendon. **(C)** Single-loop curves for measurement of maximum pullout force ($F_{\max}$), stiffness (gradient F_1 to F_2), and work to failure (area under curve) are shown.

rinsed in PBS and then soaked for 30 minutes in PBS for full rehydration.

The tendon ends were wrapped and glued (cyanoacrylate adhesive) in two saline-soaked pieces of cloth to reduce slippage and damage and fixed in clamps [15]. The suture loop was tied around a fixed metal bar connected to a 1 kN load cell (Gassmann Theiss, Bickenbach, Germany) of a universal material testing machine (Zwick 1456; Zwick GmbH, Ulm, Germany). A pullout test was performed for each suture (tested in order, medially to laterally) such that for one specimen three data points were obtained. Given the relatively large physical distance between suture loops, the local tissue surrounding each suture was unaffected by testing of other loops, and each trial was treated independently and then pooled for specimen level analysis. Specimens were preloaded at 5 N for one minute and then loaded to failure on a force-controlled basis with a speed of 1 N per second. Force (N) and displacement (mm) were recorded with dedicated software (testExpert® 10; Zwick-Roell, Ulm, Germany). Failure of the suture-tendon complex was defined as suture cutout through the tendon substance. The samples were sprayed intermittently with PBS during measurement to prevent drying.

The same testing protocol was used for tendons with an applied modified Mason-Allen stitch. For each tendon three modified Mason-Allen sutures were applied and specimens ($n = 16$) were again randomized in two groups. Samples of the crosslinking group ($n = 8$) (Fig. 1B) underwent the crosslinking procedure described above, while incubation time was varied as either 4 hours ($n = 4$) or 24 hours ($n = 4$). Tendons in the control tear group ($n = 8$) were incubated in PBS for 4 hours ($n = 4$) or 24 hours ($n = 4$). Both groups were again loaded to failure following the same protocol. Stiffness and work to failure (ie, toughness) were

calculated from derived data. Stiffness (N/mm) was calculated as gradient from 5 to 10 N for single-loop tests and from 25 to 35 N for modified Mason-Allen tests [24]. Area under the force-displacement curve from preload to maximum pullout force ($F_{\max}$) was calculated to present work to failure (J) (Fig. 1C).

Statistical Analyses

Nonparametric Mann-Whitney tests were performed for intergroup comparison of untreated and treated groups with the same incubation time at a significance level of p less than 0.05. All pairwise tests were two-sided. Results are reported as medians and range if not stated otherwise. All statistics were analyzed using PRISM Version 5.0 for Mac (Graphpad, La Jolla, CA, USA).

Results

Genipin collagen crosslinking after 24 hours incubation increased single-loop suture pullout strength, but differences after 4 hours incubation were not detected (Table 1). Pullout strength (Fig. 2) with 24 hours of genipin pretreatment was 73 N (range, 56–114 N) versus 56 N (range, 40–69 N) in the control group (difference of medians, 17 N; $p = 0.028$), with no measureable difference after 4 hours of genipin pretreatment (46 N, [range, 35–95 N] versus 45 N, [range, 28–63 N]; difference of medians, 1 N; $p = 1$) (Fig. 3). No difference in stiffness was detected after 4 hours (5.5 N/mm, [range, 3.8–7.0 N/mm] versus 5.9 N/mm, [range, 5.5–7.2 N/mm]; $p = 0.065$) nor after 24 hours (6.9 N/mm, [range, 5.0–8.4 N/mm] versus 5.8 N/mm, [range, 4.1–7.6 N/mm]; $p = 0.130$) (Fig. 4). Work to failure increased after 24 hours (373 J,

Table 1. Mechanical characteristics of infraspinatus tendons

Time of incubation (hours)	Tendon grasping technique	Pullout force (N)		Stiffness (N/mm)		Total work (J)	
		Control group	Collagen crosslinked	Control group	Collagen crosslinked	Control group	Collagen crosslinked
4	Single-loop MMA	45 (28–63)	46 (35–95)	5.9 (5.5–7.2)	5.5 (3.8–7.0)	176 (86–336)	236 (105–502)
		140 (129–151)	162 (143–193)	9.4 (7.5–10.4)	9.8 (9.0–11.9)	1020 (885–1399)	1199 (1174–1631)
24	Single-loop MMA	56 (40–69)	73 (56–114)	5.8 (4.1–7.6)	6.9 (5.0–8.4)	262 (200–349)	373 (272–805)
		164 (151–180)	172 (142–183)	10.0 (8.8–19.0)	8.8 (8.4–9.3)	1489 (993–2299)	1508 (1254–2075)

Values = median and (range); MMA = modified Mason-Allen.

[range, 272–805 J] versus 262 J, [range, 200–349 J]; $p = 0.021$) but was not different after 4 hours (236 J, [range, 105–502 J] versus 176 J, [range, 86–336 J]; $p = 0.279$) (Fig. 5). Failure mode in all tests was uniformly observed to occur through suture cutting through the tendon (knot or tendon slippage was not observed).

Using a modified Mason-Allen stitch technique in combination with genipin pretreatment, no difference in pullout strength was observed after 4 hours (162 N, [range, 143–193 N] versus 140 N, [range, 129–151 N]; difference of medians, 22 N; $p = 0.114$) nor after 24 hours of crosslinking (172 N, [range, 42–183 N] versus 164 N [range, 151–180 N]; difference of medians, 8 N; $p = 0.886$) (Fig. 3). No genipin treatment difference in the stiffness of the modified Mason-Allen sutured constructs was detected, either after 4 hours (9.8 N/mm, [range, 9.0–11.9 N/mm] versus 9.4 N/mm, [range, 7.5–10.4 N/mm]; $p = 0.486$) nor after 24 hours (8.8 N/mm, [range, 8.4–9.3 N/mm] versus 10.0 N/mm, [range, 8.8–19.0 N/mm]; $p = 0.114$) (Fig. 4). No difference was found in work to failure after 4 hours (1199 J, [range, 1174–1631 J] versus 1020 J, [range, 885–1399 J]; $p = 0.200$) or after 24 hours of crosslinking treatment (1508 J, [range, 1254–2075 J] versus 1489 J, [range, 993–2299 J]; $p = 0.886$) (Fig. 5). As with the single-loop stitch, the failure mode in all tests was uniformly observed to occur through suture cutting through the tendon (knot or tendon slippage was not observed).

Discussion

Chronic tears of the rotator cuff can cause pain and disability. If conservative treatment outcome is poor, tendon to bone repair is the preferred treatment for most patients. In addition associated rotator cuff muscle degeneration (ie, fatty degeneration, fibrosis, [31] and atrophy), tendon shortening [26] and degeneration [32] are known factors that decrease reparability and tendon to bone healing. In the majority of cases the suture-tendon interface is the weakest link of the reconstruction [7, 12, 19, 31] leading to high rates of retearing. When sutures cut through tendon, they tend to slip along the longitudinal orientation of the collagen fibers, analogous to passing a comb through a bundle of hair. Especially in arthroscopic repair, mechanically robust suture configurations (eg, modified Mason-Allen,) are technically demanding and generally too time consuming to be clinically viable [31] and even shows no superiority in clinical results [9, 20]. More simple (eg, double rows of single-loop suture) reconstruction techniques have been shown to provide adequate biomechanical strength, but also raise biological concern attributable to over-tensioning of the repair and incidence of intratendinous retearing [2]. In addition, stitch

Fig. 2A–D The graphs show the pullout force versus displacement in the best case of a tendon using single-loop stitches and modified Mason-Allen stitches. The best case of (A) genipin pretreatment was compared with the best case of the (B) control group. For the single-loop stitch, the collagen crosslinked tendon has maximum pullout forces of 146 N, 116 N, and 80 N compared with the control group tendon with maximum pullout forces of 70 N, 63 N, and 55 N. The

best case of a tendon using modified Mason-Allen stitches after 24 hours of (C) genipin pretreatment was compared with the best case of (D) the control group. For the Mason-Allen stitch, the collagen crosslinked tendon has maximum pullout forces of 217 N, 189 N, and 177 N compared with the control group tendon with maximum pullout forces of 226 N, 164 N, and 148 N.

positioning in the human rotator cuff tendon plays an important role [33]. Because tissue quality is often a critical limit to repair quality, strategies to improve intratendinous structural resistance to suture cutout (eg, crosslinking of collagen fibers) are of interest. We aimed to test the hypothesis that the traditional Chinese medicine compound genipin [14], a naturally occurring collagen crosslinker derived from the gardenia fruit, can mechanically augment tendon biomechanical properties to improve suture retention properties in an ex vivo sheep rotator cuff tear model. The most important finding of our investigation was that exogenous collagen crosslinking by genipin increased median pullout force of a simple single-loop stitch by more than 30% in a highly simplified sheep model of rotator cuff tendon repair. This increase was attained only when the rotator cuff tendon was incubated for 24 hours in a relatively high concentration solution of genipin (20 mmol/L). Genipin also increased the work to failure of the tested single-loop constructs, but apparently did not affect construct stiffness. Single-loop suture pullout differences were not observable after 4 hours of genipin

incubation. For the stronger suture configuration of the modified Mason-Allen stitches, genipin crosslinking treatment had no relevant added benefit regarding pullout characteristics, but also increased construct work to failure after 24 hours of treatment.

There are several limitations to this study that should be considered when interpreting the experimental results. First, we used healthy sheep tendons and therefore did not consider how compromised tendon tissue quality associated with tears could affect the outcome. However, the sheep infraspinatus tendon is a well-established model for investigations of rotator cuff tendon tears [4, 11, 19, 25, 32]. It also is possible and likely that the use of degenerated tendons might reveal a larger effect of genipin differences owing to increased tissue permeability and related functional effects of the applied crosslinking [16]. However, Ng et al. [28] found a greater increase in tendon modulus in bovine patellar tendons treated with genipin crosslinking compared with human patella tendons. These findings were attributed to interspecies differences in collagen properties, particularly collagen content and preexisting endogenous

Fig. 3A–B Suture pullout properties of the (A) single-loop stitch and (B) modified Mason-Allen stitch are shown. The white bars show the values of tendons in the control group and the gray bars show the values of the genipin pretreated tendons. The whiskers represent

minimum to maximum values. For single-loop configuration after 24 hours of pretreatment, an improvement ($p = 0.028$) of pullout force was observed. There was no difference in the modified Mason-Allen stitch configuration.

Fig. 4A–B Stiffness values of the (A) single-loop stitch and (B) modified Mason-Allen stitch are shown. The white bars show the values of tendons in the control group and the gray bars show the values of the genipin pretreated tendons. The whiskers represent

minimum to maximum values. No genipin treatment difference in the stiffness of either the single-loop stitch or the modified Mason-Allen sutured constructs was detected.

crosslinks. Therefore one must be cautious when extrapolating findings derived from (in vitro) animal tissue models to assumptions regarding human clinical relevance.

Our study showed potential efficacy in a novel clinical application of genipin as a naturally occurring, low-toxicity crosslinker. Genipin previously was shown to arrest mechanical progression of partial tendon tears (in vitro) in an equine superficial digital flexor tendon [15]. Fessel et al. [17] reported increased (in vitro) mechanical strength and tissue toughness of flexor tendons after 72 hours of genipin incubation. Our investigation showed feasibility and potential clinical relevance of applying crosslinking

strategies at the suture-tendon interface, at least with the single-loop stitch, anticipating that such an approach might make it possible to improve chances of successful rotator cuff repair.

A second aim of the study was to investigate whether a relevant effect might be achieved by a minimal genipin incubation time. Concerning single-loop configuration, our results indicate no functional effect of genipin crosslinking after 4 hours of incubation, and that only after 24 hours of incubation in a high-concentration genipin solution could a 30% increase in suture pullout force be achieved. Pullout forces on untreated control tendons were comparable to

Fig. 5A–B Work to failure values of the (A) single-loop stitch and (B) modified Mason-Allen stitch are shown. The white bars show the values of tendons in the control group and the gray bars show the values of the genipin pretreated tendons. The whiskers represent

minimum to maximum values. For the single-loop stitch work to failure increased after 24 hours ($p = 0.021$) but was not different after 4 hours. No difference in the modified Mason-Allen stitch configuration was detected.

results reported by Ponce et al. [29]. Despite the result that most 24-hour genipin-treated tendons performed better than untreated tendons with the single-loop stitch, we observed that there were four truly outstanding performers with almost doubled pullout force compared with the mean of the control group (Fig. 2). Reflecting the differences between the 4 hours and 24 hours incubation groups, we assume that functional differences in pullout force mostly depend on the penetration depth of genipin. Beyond qualitative visual inspection of genipin penetration depth, we did not perform quantitative histologic analysis of the tendons. Collectively, these data indicate that clinical constraints will require time-efficient and concentrated intraoperative delivery of a crosslinking agent to the suture-tissue interface. We currently are developing clinically feasible methods to accelerate and localize genipin penetration to the suture-tissue interface in an attempt to maximize functional outcome while minimizing tissue toxicity.

Finally, we could find no clear additional benefit of collagen crosslinking in combination with the relatively robust suture configuration of the modified Mason-Allen stitch. This supports the thesis that genipin application might be of more practical interest for arthroscopic rotator cuff surgery where simple or mattress stitches are commonly used.

Our experimental evidence from an ex vivo sheep shoulder model showed that exogenous collagen crosslinking by genipin can meaningfully improve single-loop stitch resistance to pullout at the tendon-suture interface. This study thus indicates potential for improving

initial tendon repair strength, and may offer potential for clinical use in arthroscopic repair of large rotator cuff tendon tears. Additional technologic development is required to establish a viable crosslinking delivery approach that can open the path to in vivo preclinical testing for safety and efficacy.

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