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Outcomes of acute Achilles tendon rupture repair with bone marrow aspirate concentrate augmentation

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Abstract
Purpose Optimal treatment of acute Achilles tendon ruptures remains controversial. Positive results using stem-cell-bearing concentrates have been reported with other soft-tissue repairs, but no studies exist on outcomes of bone marrow aspirate concentrate (BMAC) augmentation in primary Achilles tendon repair.
Methods We reviewed patients with sport-related Achilles tendon ruptures treated via open repair augmented with BMAC injection from 2009 to 2011. Data on operative complications, strength, range of motion, rerupture, calf circumference and functional improvement through progressive return to sport and the Achilles tendon Total Rupture Score (ATRS) were analysed.
Results A total of 27 patients (28 tendons) treated with open repair and BMAC injection were identified (mean age 38.3± 9.6 years). At mean follow-up of 29.7±6.1 months, there were no reruptures. Walking without a boot was at 1.8±0.7 months, participation in light activity was at 3.4±1.8 months and 92 % (25 of 27) of patients returned to their sport at 5.9±1.8 months. Mean ATRS at final follow-up was 91 (range 72–100) points. One case of superficial wound dehiscence healed with local wound care. No soft-tissue masses, bone formation or tumors were observed in the operative extremity.
Conclusions Excellent results, including no re-ruptures and early mobilisation, were observed in this small cohort with open Achilles tendon repair augmented by BMAC. No adverse outcomes of biologic treatment were observed with this protocol. The efficacy of BMAC in the operative repair of acute Achilles tendon ruptures warrants further study.
Level of Evidence: IV - Therapeutic

Keywords Achilles · Tendon · Rupture · Repair · Biologic

Introduction

Achilles tendon rupture (ATR) is a common injury [1–3], and the ideal treatment remains controversial [4–11]. Biologic augmentation is being used increasingly in the treatment of musculoskeletal soft-tissue injuries, such as chronic tendinopathies or acute ligament, muscle and tendon tears [12–16]. Platelet-rich plasma (PRP) augmentation has gained in popularity over the past 15 years, particularly in rotator cuff repair surgery [12]. The clinical outcomes in these studies have been mixed, with no clear evidence to support routine use [12–14]. A retrospective study by Sanchez et al. [15] found that PRP augmentation of Achilles tendon repair allowed for earlier return to work. A prospective cohort study by Schepull et al. [16] found no significant improvement in tendon elasticity, clinical strength or functional outcomes in repair of Achilles rupture augmented by PRP.

Although PRP delivers concentrated growth factors to the zone of tendon repair, it does not contain mesenchymal stem cells (MSC) or other progenitor cells that have been shown to improve tissue healing [17]. One approach to biologic treatment is to provide both the MSCs and platelet growth factors from a single source. Bone marrow aspirate concentrate (BMAC) contains MSCs, hematopoietic stem cells (HSCs), endothelial progenitor stem cells (EPCs) and other progenitor cells in addition to platelet-derived growth factors (PDGF) [18]. Results of animal studies have been promising, with

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improved mechanical properties and collagen composition in Achilles tendons augmented with stem cells [19, 20]. No clinical studies have yet examined the use of BMAC augmentation for tendon repair. Potential concerns with the use of BMAC, including excessive inflammatory reaction and tumor generation, have not been reported thus far in animal studies [21].

In our practice, all operatively managed acute ATRs have been augmented with BMAC since 2009. We aimed to assess the outcomes of patients treated with BMAC-augmented open Achilles tendon repair, including patient-reported outcome scores, physical examination findings, time to return to physical activity and soft-tissue complications.

Materials and methods

We performed a retrospective review of a prospectively collected database of Achilles tendon repairs done at our institution from 2009 to 2011 to identify patients who had been concomitantly treated with BMAC injection. Inclusion required that patients have acute ATRs due to recreational sport-related activity. All clinic and inpatient charts were reviewed, including operative notes, physical assessments, laboratory data and radiographic images. Institutional review board approval was obtained, and informed consent was obtained from all individual participants.

The indication for operative repair was acute ATR in each case. The senior author performed all repairs with a posteromedial approach and four-strand Krackow stitch repair using nonabsorbable no. 2 suture. In all cases, bone marrow aspirate was carefully harvested by drawing out 5 ml aliquots, then repositioning the harvesting needle. The total volume of bone marrow aspirate varied by patient, but typically ranged from 30 to 60 ml. This was kept sterile and passed off the operative field. The aspirate was then combined with a standardised mixture of anticoagulant citrate dextrose solution A (ACD-A) and separated by centrifugation at 3,200 rpm for 15 min in a specialised chamber that allows for separation of whole blood and bone marrow products (GPS III, Biomet, Warsaw, IN, USA; scientific testing and validation available on file at Biomet). The autologous plasma concentrate was then extracted manually by syringe. The aspirate was concentrated to yield a volume of 6–9 ml of BMAC. Following meticulous fluid-tight layered wound closure, the BMAC was injected directly into the repair site at various depths in order to ensure distribution around the zone of healing.

A standard postoperative protocol was applied to each patient. Immediately following the operation, patients were kept non-weight bearing in a splint in 20° of equinus for ten days. At the 10-day follow-up, patients were transitioned into a hinged controlled ankle motion (CAM) boot in 20° of plantarflexion for four weeks. Weightbearing was introduced at that first visit with a modified fencer's gait, the operative foot held near perpendicular to the direction of movement to eliminate plantarflexion. Additionally, patients were allowed to remove the boot for sleep and for gentle range-of-motion (ROM) exercises, taking care not to dorsiflex the ankle above 10° of equinus. If patients were not progressing or were unable to perform the fencer's gait at the ten day follow-up, then formal physical therapy was prescribed. At four weeks postoperatively, the patient was allowed to move the ankle to the neutral position. At six weeks postoperatively, patients were advanced to the neutral position in the CAM boot, with weight bearing as tolerated. Weaning from the CAM boot began at seven weeks, but patients were advised to avoid squatting, lunging or single-leg heel raise. The time frame for CAM boot weaning was adjusted based on the specific patient's inflammation and pain and on the intensity, duration and frequency of the patient's activity. Typically, the patients gradually increased their activity level as tolerated between three and six months. They were released to no restrictions once they were able to perform double-stance heel raise without pain or inflammation.

Patients were followed postoperatively at two weeks, six weeks, three months, six months, one year and annually thereafter. At each postoperative visit, patients were specifically assessed for calf atrophy (measured 10 cm distal to the tibial tubercle), maximum dorsi- and plantarflexion and fatigue limit during single-limb heel raise (if applicable). Functional and activity status was measured in terms of time to walking, light activity (such as cycling or jogging) and return to sport, as with the validated Achilles Total Rupture Score (ATRS) [22]. Additionally, patients were contacted via telephone to ascertain their most recent self-reported functional status, activity level and ATRS. They were monitored for the development of common postoperative complications and specifically for rerupture of the same Achilles tendon or injury to the contralateral Achilles tendon. The presence of an exaggerated inflammatory response and localised tumor formation at the wound site, both theoretical concerns with BMAC use, were monitored as well. Data were recorded and summary statistics generated using Excel.

Results

A total of 27 patients (28 tendons) were identified, with a mean age of 38.3±9.6 years at the time of surgery; there were 21 men (22 tendons) and six women (six tendons). Mean body mass index (BMI) was 27.7±3.6 kg/m^2. One of 27 patients smoked, and one had diabetes.

All patients achieved good or excellent outcomes postoperatively by attaining functional use or return to sport. At final follow-up of 29.7±6.1 months, mean calf circumference for paired operative and nonoperative extremities was 37.7±2.0

and 38.2±2.0 (difference −0.5±1.3) cm, respectively, for the 26 patients with single Achilles tendon repair. Walking without a boot was at 1.8±0.7 months, and participation in light activity was at 3.4±1.8 months. Overall, 92 % (25 of 27) patients returned to their preferred sport successfully at 5.9±1.8 months. Mean ATRS at final follow-up was 91 (range 72–100) points, with no single mean item score below 8 points. All patients were able to achieve a ROM of neutral dorsiflexion or greater and were able to successfully perform a single-limb heel raise at final follow-up. Clinical and self-reported patient outcomes are listed in Table 1.

There were few complications in the postoperative timeframe. There was one case of superficial wound dehiscence without evidence of infection that healed with local wound care. There were no noted wound infections, tendon reruptures, thromboembolic complications, injuries to the contralateral tendon or further surgeries to the operative extremity. One patient noted ipsilateral knee pain that had been associated with the original injury but denied exacerbation after the Achilles tendon repair. No soft-tissue masses, bone formation or tumors were found in follow-up examination.

Table 1 Clinical and self-reported patient outcomes following treatment with bone marrow aspirate concentrate (BMAC)

Clinical and self-reported patient outcomes	
Variables	Mean (range)
Mean follow-up (months)	29.7 (24.0 to 45.4)
Mean difference in calf circumference[a] (cm)	−0.5 (−2.0 to 3.0)
Time to walking without boot (months)	1.8 (0.8 to 3.5)
Time to light activity (months)	3.4 (1.2 to 10.0)
Time to return to sport (months)	5.9 (3.0 to 9.0)
Returned to sport	92 % (25 of 27)
Mean ATRS (points)	91 (72 to 100)
Injury mechanism	
Basketball	10
Tennis	4
Soccer	2
Running	2
Squash	2
Baseball	1
Volleyball	1
Climbing stairs	1
Diving	1
Exercising	1
Fall	1
Gymnastics	1
Jumping rope	1

ATRS Achilles Tendon Total Rupture Score

[a] Measured 10 cm below tibial tubercle; difference=operative vs. nonoperative

Patient self-reported outcomes after surgery were largely positive. At final follow-up, no patients reported any unresolved pain in the operative leg or from the aspiration site.

Discussion

Excellent functional outcomes and a high rate of return to sport were found in this case series after open Achilles tendon repairs augmented with BMAC injection. Such augmentation is not standard practice, and the study demonstrates the feasibility of this novel technique. There were no major adverse events or outcomes related to either the procedure or the BMAC injection. Successful functional outcomes in terms of rehabilitation progression, return to sport and performance of single-limb heel raise all support overall good clinical outcomes. This study is among the first to demonstrate such results using BMAC and in the testing of our standardised regimen for its creation and use. Precise chemical activation, centrifugation and methodical injection allowed us to reproducibly create a viable, stem-cell-bearing concentrate. Although prior work with biologic augmentation with platelet growth factors in rotator cuff repair has been equivocal, we believe this is due to the absence of stem cells and other mononuclear progenitor cells in PRP. While routine use of BMAC is not yet commonplace and should be regarded as a technique in development, this preliminary study opens the door for further investigation into BMAC as a useful adjunct in Achilles rupture repair.

Several limitations exist in our study, principally due to the retrospective design and lack of a control group, with the latter preventing us from separating the effect of BMAC from the effect of early mobilisation. While our tendency to prescribe early rehabilitation after Achilles repairs has been encouraged by our experience with BMAC in the laboratory setting, this study alone cannot elucidate the effects of each treatment. The cohort size that received BMAC was small, and all outcomes must therefore be interpreted in light of this limitation. Infrequent complications of Achilles repair surgery, such as venous thromboembolism, cannot be adequately studied with this sample size. Furthermore, the techniques for BMAC harvest, production and delivery are in their infancy, and while our centre has achieved reproducible results from a standard regimen, this may not be generalisable to other treatment protocols. Despite our success, caution and further research are warranted before employing BMAC for Achilles tendon repairs on a routine basis. Follow-up in this study was short, and long term-results will be necessary to further characterise the clinical outcomes described here.

Animal studies of Achilles tendon repairs have reported superior biomechanical and histological results with biologic augmentation. Urdzikova et al. [21] used a MSC injection to augment nonoperative Achilles tendon healing in 81 rats (41

tendons with, 40 without, MSC injection). They demonstrated improved vascularisation and more normal histological organisation in the MSC-augmented tendons. Yao et al. [20] studied the effects of MSC-coated suture to augment Achilles repair in 105 rats. They reported increased strength compared with standard suture repair at early time points (12.6 vs. 8.6 N and 21 vs. 16 N at seven and ten days, respectively), and hypothesised that stem cell augmentation may improve early mechanical properties in tendon repair and "jump-start" the repair process. In a similar report on MSC-bearing adjuncts, Adams et al. [19] studied the effects of suture alone (36 tendons), suture plus stem-cell-concentrate injection (36 tendons) or stem cell-loaded suture (36 tendons) in the repair of 108 rat Achilles tendons. When animals were sacrificed at 14 days, tendons from those in the suture-alone group had a lower ultimate failure load (mean 1.3 vs. 3.0 vs. 3.2 N/mm^2, respectively). Constructs with stem-cell-bearing suture also exhibited better collagen orientation and fewer fibroblasts on histology than the other two groups at up to 28 days. Another study on rat tendon ruptures using a large-gap-defect model demonstrated that MSCs loaded into a surgically implanted mesh showed enhanced healing [23].

Many mechanisms have been proposed regarding the role of BMAC in tendon healing. Cytokines from platelets produced by BMAC cells modulate the healing response by controlling inflammation, reducing fibrosis and recruiting other cells, including tenocytes and mesenchymal stem cells, as suggested by work demonstrating the ability of interleukins 4 and 13 to promote proliferation of the primary human tenocytes [24]. BMAC has previously been shown to contain hematopoietic and osteogenic growth factors, including vascular endothelial growth factor, platelet-derived growth factor and transforming growth factor beta [25]. While the underlying mechanism for ATR is not fully understood, it is generally accepted that ruptures occur in previously abnormal but often asymptomatic tendons [26], some of which may have a dysvascular component [27] and as such may benefit from adjunctive biologic supplementation.

The clinical outcomes of our cohort also compare favorably with those of previous studies. As a historical control, patients in a large randomised controlled trial [28] of operative repair with early aggressive physical therapy (49 patients) vs. nonoperative treatment (51 patients) of acute ATRs demonstrated mean ATRS scores at one year of 82 (range 0–100) and 80 (range 2–100) points, respectively. While our reported ATRS results are slightly higher, our cohort is smaller and sustained no postoperative rupture complications, which would reduce the mean ATRS (the cited study reported one partial re-rupture in the operative group and five re-ruptures in the nonoperative group). Indeed, the median ATRS scores in the cited study more closely match our results (89 and 90 points, respectively). Sanchez et al. [15] used PRP-augmented Achilles tendon repair to treat six patients with acute ruptures. These patients recovered baseline ROM earlier and returned to running sooner than controls, who received no PRP (seven vs. 11 weeks, and 11 vs. 18 weeks, respectively). In our study, mean time to running was 3.4 months, with some beginning light jogging activity as early as one month.

Our study stands in contrast to a previous report that attributed detrimental effects of biologic enhancement of Achilles rupture repairs. Shepull et al. [16] randomised 26 patients who had acute ATR to tendon repair with postprocedure injection of 10 ml PRP (16 patients) or without any injection (14 patients). These investigators reported one rerupture and one deep infection in the PRP group and no difference in heel raise index at 1 year. They reported a significantly lower mean ATRS score in the PRP group compared with controls of 78 (range 75 to 85) vs. 89 (range 83 to 92) points at one year, respectively. Importantly, Shepull et al's. study was powered to study differences in heel raises rather than ATRS. Furthermore, while early weight bearing was permitted, aggressiveness of postoperative physical therapy was unclear (cast off at seven weeks but plyometrics not permitted until week 16, jogging until week 18 and sport until at least five months).

Similar excellent results have been reported without the use of biologic augmentation, and thus the promise of this approach may depend on defining its appropriate application. With more rapid tendon consolidation, surgeons may consider permitting earlier aggressive therapy and weight bearing. As early mobilisation risks re-rupture from loss of tendon–tendon and tendon–bone cohesion, tendon lengthening, gap formation or delay of healing, a biologic augmentation strategy is an attractive solution to address all potential mechanisms of failure. Future studies in larger cohorts may better elucidate the effects of BMAC on rates of repair failure, as none were seen in our study, or on long-term prevention of rerupture. The efficacy of BMAC in the operative repair of acute ATRs warrants further study.

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