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Effects of Cryopreserved Amniotic Membrane-Umbilical Cord Allograft on Total Ankle Arthroplasty Wound Healing

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ABSTRACT

Relatively high rates of wound healing complications continue to be reported with a total ankle arthroplasty (TAA) anterior incision. The amniotic membrane-umbilical cord (AM-UC) allograft is a regenerative orthobiologic adjunct that modulates wound healing by down-regulating inflammation, enhancing local healing and antimicrobial factors, and reducing scar formation. The purpose of this study was to determine whether local application of a cryopreserved AM-UC allograft enhances soft tissue healing after TAA. A total of 104 patients with symptomatic ankle arthritis who failed conservative management underwent standard TAA. At skin closure, patients were allocated to either the treatment (local application of AM-UC) or control (no allograft) group. Demographic data, patient comorbidities, and radiographic findings were collected. The primary outcome was a major complication necessitating reoperation. Secondary outcomes were time to healing, minor complications (i.e., skin dehiscence, local wound care, use of antibiotics), and patient scar assessment. Local application of an AM-UC allograft significantly decreased the overall time to skin healing (28.5 days vs 40 days; $p = .03$). Two patients required a reoperation for soft tissue wound complications, with no difference ($p = 1.00$) between the groups. No statistically significant difference was detected in terms of skin dehiscence, local wound care, or antibiotic prescriptions in the 2 groups. Regenerative technology using local application of a cryopreserved AM-UC allograft may enhance TAA outcomes by decreasing the time to healing. Larger randomized controlled trials are needed to determine whether an AM-UC allograft enhances soft tissue wound healing and ultimately reduces the incidence of devastating soft tissue complications.

Despite improvements in newer-generation total ankle arthroplasty (TAA) implants, relatively high complication rates continue to be reported with the anterior ankle incision. Only 14% to 66% of anterior incisions heal without wound healing complications. Minor complications requiring local care and/or oral antibiotics occur in 6% to 30% of patients, and major complications necessitating reoperation occur in 6% to 9% of patients undergoing TAA through an anterior incision (1–5). The importance of meticulous soft tissue dissection, careful handling, postoperative monitoring, and progressive mobilization with physical therapy (after early wound healing) are critically important for minimizing wound complications following surgery. Techniques to decrease postoperative soft tissue complications described in the literature include a compression wrap protocol (6), negative pressure wound therapy (3), and continuous external tissue expanders (7). Other methods supported by expert opinion to decrease the risk of postoperative soft tissue complications following TAA include postoperative elevation of the lower extremity, limited weight bearing, and use of an appropriately fitted cast or prefabricated orthotic. Factors known to increase the risk of postoperative infection and wound breakdown after foot and ankle surgery include a history of diabetes (1,8), peripheral vascular disease (1), previous surgeries close to the anterior TAA incision site (1), tobacco use (9), obesity (10,11), use of wound-compromising medications (12), and postoperative noncompliance (13).

Recently, multiple regenerative orthobiologic adjuncts have been investigated for their ability to reduce postoperative complications by enhancing local healing factors and reducing the risk of infection. The use of adjunctive therapy using cryopreserved amniotic membrane-umbilical cord (AM-UC) allografts modulates wound healing by down regulating inflammation, enhancing local growth and antimicrobial factors, and reducing scar formation (14–20).

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Basic Science of AM-UC Allograft

Amniotic membrane and umbilical cord tissues are well known for their therapeutic potential. Amniotic tissue (1) contains an extracellular matrix that acts as a natural scaffold for cellular migration and adhesion, as well as structural support for cells (2); contains collagen types I, III, IV, V, and VI, hyaluronic acid, and multiple growth factors; and (3) has antimicrobial properties (e.g., β-defensins) (21,22). Local application of a cryopreserved amniotic membrane allograft has the potential to accelerate and enhance healing through its ability to prevent inflammation (15–18), inhibit the inflammatory cascade, and disrupt the link between inflammation and cicatricial progression (19,20,23–25). Furthermore, amniotic membrane has demonstrated low immunogenicity given the lack of expression of HLA-A, -B, -C, and -DR antigens and β2-microglobulin (26,27). It has been shown to decrease inflammation by inhibiting cytokine signaling mechanisms (15), decreasing the lifespan of proinflammatory cells by promoting selective apoptosis (16,17), and inhibiting the infiltration and proliferation of inflammatory cells (18). In addition, local application of amniotic membrane has shown the ability to disrupt the cycle connecting inflammation and scar by decreasing TGF-β signaling (19), inhibiting cytokines such as tumor necrosis factor-α in the presence of dendritic cells (28), and decreasing the infiltration, proliferation, and differentiation of fibroblasts (20,29). Amniotic membrane prevents apoptosis, promotes migration and adhesion, and helps maintain the normal morphology of epithelial cells (30,31). Amniotic tissue has the ability to attenuate the "cytokine storm" following injury, which may be advantageous in healing and scar formation (32). Umbilical cord tissue contains glycosaminoglycan-rich Wharton's jelly and unique matrix complexes formed by a covalent linkage between hyaluronan and heavy chain 1 of the inter-α-trypsin inhibitor pentraxin-3, responsible for its therapeutic action (33–35).

Clinical Application of AM-UC Allograft

Historically, placental allografts were used more liberally in the early 1900s for skin grafting, burn treatment, and ulcerative wound care. Owing to fears of potential disease transmission and immunoreactivity with contaminated tissue, the use of freshly acquired amniotic tissue abruptly ceased (36). Following the application of newer tissue processing techniques to reduce the risk of these concerns, various subspecialties have begun to reevaluate the possible utility of AM-UC allografts. Currently, local application of cryopreserved AM-UC allografts is used primarily in wound care (i.e., burn and chronic nonhealing ulcerative wound care) and ophthalmology (e.g., ocular thermal and chemical injuries). Several randomized controlled trials have documented significant improvements in healing in ocular chemical burns, venous stasis ulcerative wounds, and diabetic wounds using amniotic membrane allografts (37–41). In addition, allogenic AM-UC has been used in small series of patients with chronic plantar fasciitis and Achilles tendinosis (42), as well as following neurolysis with an AM-UC nerve wrap (43).

Regenerative technology using local application of cryopreserved AM-UC allograft may enhance TAA outcomes by decreasing devastating major (i.e., requiring reoperation) and minor (i.e., skin dehiscence, local wound care, and use of antibiotics) soft tissue complications, decreasing time to healing, and improving patient scar assessment. To our knowledge, no previous study has addressed the local wound healing potential of cryopreserved AM-UC allograft to enhance wound healing in the ankle. The purpose of this study was to determine whether the local application of cryopreserved AM-UC allograft can enhance soft tissue wound healing of the TAA anterior ankle incision. Our hypothesis was that the incidence of minor and major complications, time to healing, and patient scar assessment would improve in the general population undergoing TAA, and that patients with specific risk factors would demonstrate an even greater reduction in wound complications with local application of cryopreserved AM-UC allograft.

Patients and Methods

Approval for this retrospective comparative cohort study was obtained from our Institutional Review Board before study initiation. All patients undergoing TAA by the senior authors (R.B.B. and W.H.D.) between November 1, 2014, and August 1, 2016, were included in the study. No patients were excluded. Patients with symptomatic ankle arthritis who failed conservative management underwent TAA concomitantly at a single tertiary hospital by 2 senior foot and ankle surgeons with comparable experience in both the application of AM-UC and TAA, with >20 years of experience in TAA (>600 cases each). Both senior surgeons were present and involved in all surgeries, and all patients underwent the same procedure, as indicated by their pathology, postoperative regimen, and rehabilitation protocol. At skin closure, patients were allocated to either the treatment group (cryopreserved AM-UC allograft; Clarix, Amniox Medical, Atlanta, GA) or control group (no allograft). The decision to use an AM-UC allograft was based solely on which surgeon was designated the primary surgeon (determined by who preoperatively evaluated and scheduled the patient for surgery) on the operative report, to ensure an accurate and more easily obtainable historical record. All patients under the care of 1 surgeon (W.H.D.) received an AM-UC allograft. The skin closure of the treatment group was performed in standard fashion with local application of cryopreserved AM-UC overlying the extensor retinaculum layer. Fig. 1 shows an example of an allograft onlay. No allograft was used for the control group.

The following data were obtained for each patient: age, sex, body mass index, race, smoking history, history of diabetes, insulin dependency, date of surgery, laterality, local application of AM-UC allograft, history of previous arthrodesis, diagnosis (i.e., primary/idiopathic, secondary/posttraumatic, rheumatoid), and coronal and sagittal alignment preoperatively and postoperatively. All charts were reviewed independently, and all data were collected by a single author (T.B.B.), who did not participate in patient care or surgery.

Given the possible risk of complications associated with large coronal and sagittal corrections, changes in coronal and sagittal alignment were evaluated in the treatment and control groups to identify and avoid any potential for confounding variables (44,45). All radiographic measurements were performed by a single author (T.B.B.). All coronal and sagittal radiographic measurements followed published techniques (46). Coronal

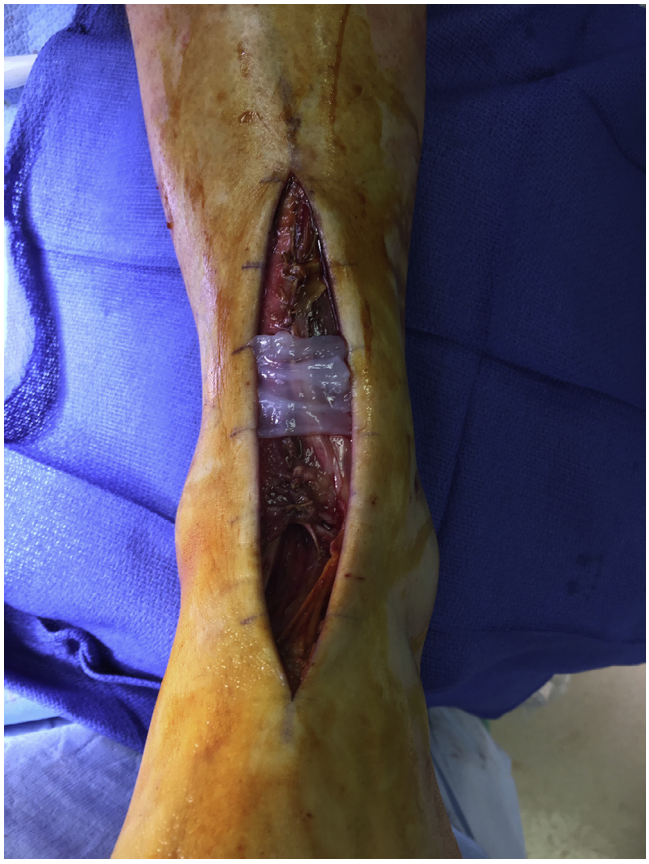

Fig. 1. Amniotic membrane-umbilical cord allograft only over the extensor retinaculum.

ankle alignment was determined on weight-bearing anteroposterior radiographs in neutral plantarflexion by measuring the angle between the vertical axes of the tibial shaft and talus preoperatively and the tibial stem and talar components postoperatively. Sagittal alignment was determined on weight-bearing lateral radiographs in neutral plantar flexion by measuring the difference between the vertical axes of the tibial shaft and a line perpendicular to the tibial intramedullary canal preoperatively and the angle between the anatomic axis and the final implant axis postoperatively. Varus and procurvatum were reported as positive angles. Clinically significant coronal and sagittal correction were recorded as changes <-5° or >5°.

The primary outcome was a major complication requiring reoperation. All patient charts were reviewed to identify the reason for reoperation. Secondary outcomes were time to healing, minor complications, and the Patient Scar Assessment Scale (PSAS). Time to healing was measured as the difference between the date of surgery and the date of noted wound healing. Minor complications were defined as skin dehiscence, local wound care, and use of antibiotics postoperatively. Outcome assessments were obtained by reviewing the charts by a single author (T.B.B.).

Given the retrospective nature of the study, clinical outcome measures were based on the following criteria. Wounds were considered healed when all of the following criteria were met: sutures or staples were removed; no additional local wound care, dehiscence, or antibiotic prescriptions were noted in the chart; and the clinical note explicitly documented wound healing. The wound was defined as completely healed when it was epithelialized with no evidence of necrosis, dehiscence, cellulitis, or eschar. Local wound care included enzymatic debridement with collagenase, mechanical or sharp debridement in the office setting, or application of wet-to-dry dressings. Antibiotics were considered administered if topical, intravenous, or oral antibiotics were prescribed postoperatively.

Given the potential for enhanced wound healing with scar inhibition, we obtained the PSAS score, a component of the Patient Observer Scar Assessment Scale (version 2.0), for the treatment and control groups. The PSAS is a free, publicly available, validated 6-item questionnaire designed to measure patients' satisfaction about their scars (47). The questionnaire elicits the patient's subjective assessment of scar quality, including width, color, elevation, and overall appearance. Using an Institutional Review Board–approved telephone or e-mail script, a member of the research staff contacted patients to obtain PSAS scores following confirmation that the surgical site was healed. All domains were graded by the patient on a 10-point scale, with 1 indicating the best or most normal result and 10 indicating the worst or most disfiguring result. A cumulative score of 6 corresponds to normal skin, and 60 is the worst scar imaginable to the patient.

Statistical Analysis

Standard descriptive statistics are reported. For bivariate analyses, the Fisher exact test was performed to compare primary and secondary outcomes of patients undergoing TAA in the treatment group (AM-UC allograft) and control group (no allograft). Differences between the treatment and control groups were assessed with the Wilcoxon test, given nonnormally distributed data, to determine associations of these variables and TAA treated with AM-UC vs no allograft. Median values with interquartile range (IQR) are reported for nonnormally distributed data. Statistical significance was set at $p < .05$ with associated 95% confidence intervals. Separate stepwise logistic regression models were performed for all independent variables with a threshold p value of .10 against the primary outcome of major complications in addition to secondary outcomes (i.e., time to healing, dehiscence, antibiotic, and wound care). Statistical analysis was performed by 2 authors (T.B.B., S.M.O).

Results

Of the 104 patients who underwent TAA between November 1, 2014, and August 1, 2016, 54 were allocated to the treatment group and 50 were allocated to the control group (no allograft). The median duration of patient follow-up was 349 (range, 21 to 966) days. No follow-up was available for 2 of 104 patients (1.92%), who were returned to hometowns of Costa Rica and Wisconsin immediately following hospital discharge. The median age was 59.5 (IQR, 55 to 66) years in the AM-UC group and 66.5 (IQR, 60 to 71) years in the control group ($p = .0018$). There was a statistically significantly higher percentage of patients with a history of diabetes who received AM-UC than those who did not receive the adjunct therapy (20% vs 2%; $p = .01$). Other than age and history of diabetes, the groups were considered fairly homogenous given that with the numbers available, no statistically significant difference between the 2 groups could be detected with respect to body mass index, sagittal or coronal correction, sex, history of smoking, previous arthrodesis, diagnosis, and primary or revision procedure. Table 1 provides patient demographic and comorbidity data.

Major complications were reported in 11 patients (10.78%) requiring reoperation. Major complications were reported in 5 patients (10%) in the control group and in 6 patients (11.53%) in the AM-UC group. However, there were only 2 reoperations (1.92%) specifically for wound complications. Patient outcomes are summarized in Table 2. In the control group, a subcutaneous abscess developed overlying the anterolateral aspect of the ankle 198 days after the initial procedure over the proximal aspect of the prior incision. The hardware was retained, and the infection was cleared with irrigation and debridement and i.v. antibiotics. In the treatment group, a young female with rheumatoid arthritis and scleroderma on methotrexate, plaquenil, and chronic prednisone therapy developed a recurrent draining sinus after staged revision TAA and flap coverage with healing obtained via irrigation and debridement, polyethylene liner exchange, and lifelong suppressive antibiotics. Other reasons for reoperation included 2 cases of instability and a single case of aseptic talar subsidence, equinus contracture and stiffness, osteolysis and hardware loosening, nonunion with triple arthrodesis, subcutaneous abscess, screw removal, medial malleolus stress fracture, and avascular necrosis of distal tibia. Wound healing

Table 1
Patient demographics and comorbidities in the general total ankle arthroplasty population and the control and amniotic membrane-umbilical cord allograft groups

Parameter	Overall (N = 104)	Control (n = 50)	AM-UC (n = 54)	*P* Value, Control vs AM-UC
Clinical factors, n (%)				
Diagnosis				
Primary (idiopathic)	57 (54.8)	24 (48)	33 (61.0)	.24
Posttraumatic	41 (39.4)	22 (44)	19 (35.0)	.42
Rheumatoid arthritis	6 (5.8)	4 (8)	2 (3.7)	.42
Age >65 y	41 (39.4)	27 (54)	14 (25.9)	.004*
Female sex	37 (35.5)	15 (30)	22 (40.7)	.31
Obesity	48 (46.1)	22 (44)	26 (48.1)	.70
Diabetes mellitus	10 (9.6)	1 (2)	9 (20.0)	.02*
Insulin-dependent	4 (3.8)	0 (0)	4 (7.4)	.11
Previous arthrodesis	20 (19)	11 (22)	9 (16.7)	.62
Revision TAA	15 (14)	4 (8)	11 (20.3)	.10
Smoking status				
Current or former	42 (40.3)	22 (44)	20 (37.0)	.55
Never	62 (59.6)	28 (56)	34 (63.0)	.55
Operative factors				
Sagittal correction, °, median (IQR)	2 (−1 to 6)	3 (−1 to 9)	2 (−2 to 5)	.13
Coronal correction, °, median (IQR)	0 (−5 to 6)	0.5 (−5 to 10)	−1 (−5 to 3)	.42

Abbreviations: AM-UC, amniotic membrane-umbilical cord; IQR, interquartile range; TAA, total ankle arthroplasty.
* Level of statistical significance ($p = .05$).

Table 2
Outcomes in the control and amniotic membrane-umbilical cord allograft groups

Outcomes	Control (n = 50)	AM-UC (n = 52)	*P* Value
Primary outcomes, n (%)			
Total reoperations	5 (10)	6 (11)	1.00
Reoperations for soft tissues	1 (2)	1 (1.9)	1.00
Secondary outcomes			
Time to healing, d, median (IQR)	40 (27 to 81)	28.5 (18.5 to 56.5)	.03*
Minor complications, n (%)			
Wound care	8 (16)	10 (18.5)	.99
Dehiscence	6 (13)	3 (6)	.29
Antibiotic prescription	11 (22)	5 (9)	.09
PSAS score, median (IQR)	7 (2 to 19)	10 (5 to 25)	.08

Abbreviations: AM-UC, amniotic membrane-umbilical cord; IQR, interquartile range; PSAS, Patient Scar Assessment Scale.
* Level of statistical significance ($p = .05$).

was achieved without complications in 86 of our patients (84.31%). Local application of AM-UC allograft significantly decreased the overall time to skin healing (from 40 days to 28.5 days; $p = .037$). Overall, minor complications were reported in 18 patients (17.64%). Skin dehiscence requiring local wound care occurred in 18 (17.64%) patients, and antibiotics were prescribed in 15 (14.70%) patients. Skin dehiscence was reported in 6 patients (12%) in the control group and 3 patients (5.77%) in the AM-UC group ($p = .29$). Antibiotic prescription was reported in 11 patients (22%) in the control group compared with 5 (9.61%) in the AM-UC group ($p = .09$). Local wound care was reported in 8 patients (16%) in the control group compared with 10 (19.23%) in the AM-UC group ($p = .99$). The median PSAS score was 10 (IQR, 5 to 25) for the treatment group and 7 (IQR, 2 to 19) for the control group ($p = .08$). We found no statistically significant between-group differences in the rates of antibiotic prescribing, skin dehiscence, local wound care, or PSAS.

Secondary analyses of possible risk factors for local wound care complications were performed, and between-group differences with respect to major complications, time to healing, and rates of minor complications were noted (Table 3 and Fig. 2). The analysis of risk factors revealed differences in rates of minor complications that were inadequately powered to demonstrate statistical significance, and thus these values were not reported.

Discussion

In our modern era of medicine with transition from a fee-for-service model of healthcare reimbursement toward value-based purchasing with bundled payments and accountable care, judicious and economical use of resources is being more critically appraised. Universal local application of cryopreserved AM-UC allograft might not be appropriate or predictably improve patient outcomes in all demographics and populations. However, appropriate patient selection with the use of regenerative adjunct technologies may benefit patient outcomes and reduce morbidity and possible mortality in patients with known risk factors for wound complications.

Risk factors known to increase risk of postoperative infection and wound breakdown in patients undergoing foot and ankle surgery include a history of diabetes (1,8), peripheral vascular disease (1), previous surgeries close to the anterior TAA surgical site (1), tobacco use (9), obesity (10,11), wound-compromising medications (12), and postoperative noncompliance (13). In 2010, Wukich et al (8) compared postoperative infection rates in patients with and without diabetes and reported that a delay in wound healing increased the risk of operative site infections. In patients treated for ankle fractures with open reduction and internal fixation, overall charges were significantly higher in patients whose postoperative course was complicated by infection, resulting in significantly higher total charges ($128,122 vs $49,983) (48). A direct reduction in patient complications will reduce the overall cost of care by decreasing the time to healing, the risk of readmission, and the rates of minor and major complications. Therefore, it is beneficial to review patient cohorts to identify possible candidates for regenerative adjunct therapy.

The need for wound healing to create a biological barrier for infection is critical. Patton et al (49) reviewed 966 patients who underwent TAA and demonstrated that a delay in wound healing of more than 14 days postoperatively dramatically increased the risk of infection in patients undergoing TAA. Given the known impact of delayed wound healing on the risk of infection and complications associated with TAA,

Table 3
Comparison of secondary outcomes with known risk factors in the control and amniotic membrane-umbilical cord allograft groups

Outcome	Time to Healing, d, median (IQR)		Wound Care, n (%)		Dehiscence, n (%)		Antibiotics, n (%)	
	Control (n = 50)	AM-UC (n = 52)	Control (n = 50)	AM-UC (n = 52)	Control (n = 50)	AM-UC (n = 52)	Control (n = 50)	AM-UC (n = 52)
Overall	40 (27 to 81)	29 (21 to 57)	8 (17)	10 (19)	6 (13)	3 (6)	11 (23)	5 (9)
Clinical risk factors								
Obesity	40 (27 to 76)	29 (27 to 40)	4 (18)	4 (15)	2 (9)	1 (4)	6 (27)	1 (4)
Age >65 y	43 (28 to 78)	28 (23 to 32)	5 (17)	2 (13)	3 (10)	1 (6)	5 (17)	2 (13)
Diabetes mellitus	92 (92 to 92)	57 (28 to 74)	1 (100)	3 (33)	1 (100)	1 (11)	1 (100)	1 (11)
Revision	28 (27 to 38)	45 (25 to 60)	1 (20)	3 (27)	0 (0)	2 (18)	0 (0)	2 (18)
Female sex	34 (26 to 77)	28 (15 to 33)	2 (13)	4 (18)	1 (7)	2 (9)	4 (27)	3 (14)
Male sex	43 (28 to 83)	30 (27 to 69)	6 (18)	6 (10)	5 (15)	1 (3)	7 (21)	2 (6)
Smoking status	51 (31 to 91)	28 (27 to 51)	5 (24)	5 (26)	3 (14)	3 (16)	5 (24)	4 (21)
Insulin use	*	28 (28 to 69)	*	1 (25)	*	1 (25)	*	1 (25)
Operative risk factors								
Sagittal correction ($\leq -5°$, $\geq 5°$)	41 (28 to 66)	29 (16 to 56)	2 (7)	3 (16)	1 (4)	1 (5)	2 (7)	2 (11)
Coronal correction ($\leq -5°$, $\geq 5°$)	43 (28 to 82)	29 (24 to 69)	3 (10)	5 (19)	2 (6)	1 (4)	4 (13)	2 (8)

Abbreviations: IQR, interquartile range; AM-UC, amniotic membrane-umbilical cord.
* No patients in the subgroup analysis.

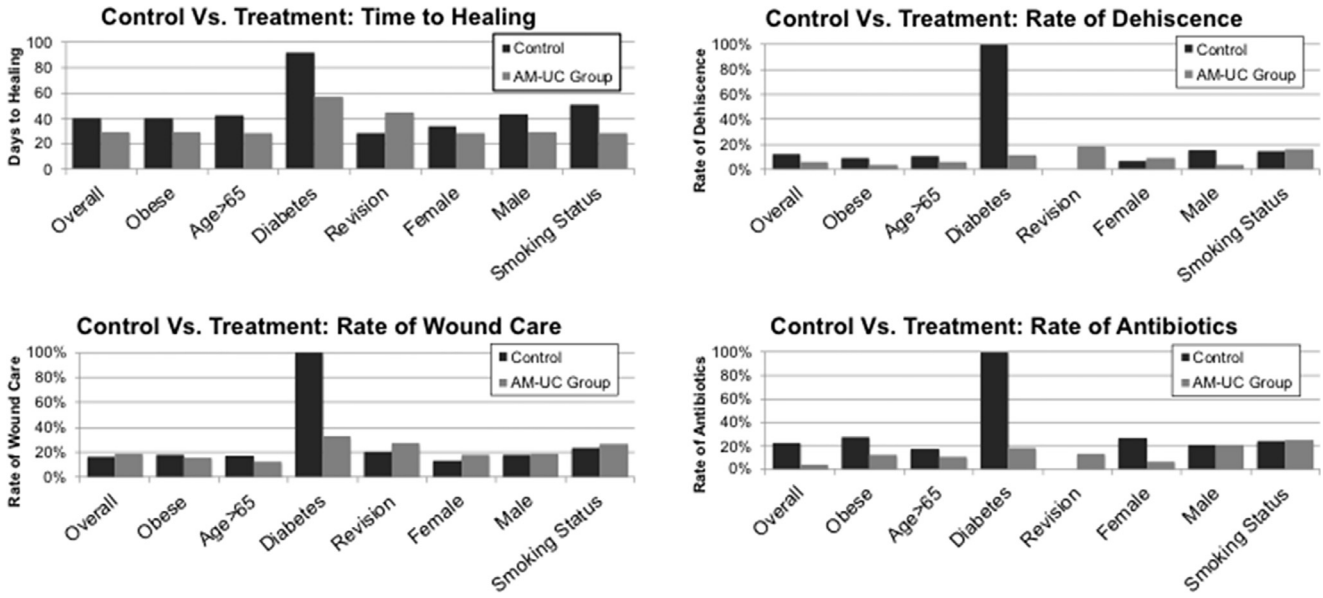

Fig. 2. Time to healing, rate of dehiscence, rate of wound care, and rate of antibiotic use in the treatment and control groups.

methods to decrease time to healing are of clinical importance. In our study, patients who underwent TAA with local application of AM-UC allograft healed a median of nearly 2 weeks earlier than those treated with traditional closure alone. This difference increased to 7 weeks earlier in patients with diabetes mellitus and >3 weeks earlier in patients with a current or previous history of smoking. However, given the small numbers in our cohort, the differences did not reach statistical significance.

The median PSAS was 10 (IQR, 5 to 25) for the treatment group compared with 7 (IQR, 2 to 19) for the control group ($p = .08$). Given that the score for normal skin is 6 and the worst imaginable score is 60, the difference in PSAS is not statistically significant and certainly does not reach the minimal clinical important difference (MCID) suggested in previous work (50). Although AM-UC has been proposed to enhance wound healing, there was no difference in PSAS between the treatment and control groups.

The strengths of this study include our relatively large cohort of patients undergoing TAA treated with adjunct AM-UC allograft. The overall reported outcomes in our control group were similar to previously published results. Confounding variables were minimized given a single institution with standardized procedures, follow-up, postoperative regimen, rehabilitation protocol, and staff. Although physician assistants who were primarily responsible for assessing wound healing in the early postoperative follow-ups were not blinded, there was no evidence of AM-UC allograft use other than a single line in the operative report, which physician assistants do not routinely read in our practice. We attempted to minimize nonresponder bias, and only 2 of 102 patients (1.9%) were lost to follow-up during the study period. Our secondary outcomes (i.e., time to healing; rates of dehiscence, wound care, and antibiotic prescription; and PSAS score) were assessed and prescribed consistently in each patient by the same attending physicians or physician assistants.

Although not adequately powered to determine statistical significance among our treatment vs control groups, this study is critical to providing preliminary pilot data for which future studies may be further justified and may serve as a baseline for determining necessary sample sizes to adequately power larger prospective randomized controlled studies. We hope that the publication of this study will make it possible to narrow the focus on potential patient populations that would benefit from regenerative adjuncts in TAA and aid in estimating the sample sizes necessary to determine enhanced healing. Our study does not support the use of regenerative adjuncts for routine TAA but provides preliminary data supporting the possible utility of biologics in high-risk, complicated patient populations undergoing TAA, including patients with diabetes, obesity, and a history of smoking.

Limitations of this study include the retrospective design, which is subject to statistical bias. In an attempt to minimize statistical bias, we included all patients operated on by both senior foot and ankle attendings. All patients who did not receive local application of cryopreserved AM-UC were included in the control group rather than attempting to match them. Retrospective studies rely heavily on the accuracy of the medical record, and the integrity of the data for analysis is dependent on the documentation within the electronic medical record. The small number of major and minor complications made the statistical analysis difficult to interpret. In addition, the degree to which the external validity is applicable is uncertain, given that our study was conducted at a single center by 2 senior orthopedic surgeons (R.B.B., W.H.D.). Several risk factors may play a role in time to healing and wound complications; we attempted to address these factors through proper statistical analysis. However, although we were able to identify and differentiate patients with insulin-dependent diabetes mellitus and patients with non–insulin-dependent diabetes mellitus, we were unable to evaluate the effects of blood glucose or glycohemoglobin (Hgb A1C) levels. It is well known that patients with poorly controlled diabetes of longer duration are more likely to experience complications (51). Therefore, our inability to stratify the patients with diabetes based on glycemic control and the duration of disease is another weakness of this study. Nonetheless, despite our appreciation of the limitations of our investigation, we believe that our results will be useful in the future development of prospective cohort studies and randomized controlled trials focusing on determining potential patient populations that would benefit from the use of AM-UC allograft.

In conclusion, the present study demonstrates a statistically significant advantage of local application of cryopreserved AM-UC allograft over traditional closure in terms of time to healing. Regenerative orthobiologic technology using local application of cryopreserved AM-UC allograft can enhance TAA outcomes by decreasing time to healing. Larger randomized controlled trials are needed to determine whether local application of cryopreserved AM-UC allograft can enhance soft

tissue wound healing and ultimately reduce the incidence of devastating soft tissue complications. Further studies may be warranted, and larger prospective randomized controlled trials are recommended to study high-risk patient populations.

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