

An Open-label, Single-center, Retrospective Study of Cryopreserved Amniotic Membrane and Umbilical Cord Tissue as an Adjunct for Foot and Ankle Surgery

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ABSTRACT

The primary aim of this study was to compare preoperative assessments with postoperative outcomes from patients undergoing foot and ankle revisions and/or complex reconstructions with tendon and/or nerve involvement using cryopreserved human amniotic membrane and umbilical cord (cHAM/UC). We hypothesized complex foot and ankle surgery using amniotic membrane would be an effective treatment leading to reduced pain and improved functional outcomes. Fourteen patients (6 male and 8 female) underwent open foot and ankle surgery during the study period. All 14 patients included in this cohort reported improvement, namely, lessened pain intensity both on the American Orthopedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale and the pain numeric rating scale (NRS), as well as improved functional status. The mean AOFAS score improved from 50 (range, 17–79) preoperatively to 85 (range, 67–100) postoperatively. The mean NRS score also improved from 8 (range, 4–10) preoperatively to 2 (range, 0–6) postoperatively with a mean percent change in pain NRS of 78% (range 17–100%). Both outcome-scoring systems showed statistically significant differences ($p < .0001$) when we compared the preoperative and postoperative results. All patients included in the cohort showed improvement in both outcome measures. Further study of long-term endpoints is warranted.

INTRODUCTION

Amniotic membrane (AM) and umbilical cord (UC) tissues share the same cell origin as the developing fetus and are rich in growth factors, cytokines, and both structural and non-structural proteins.^{1,2-6} High molecular weight (HMW) hyaluronic acid (HA) is the primary glycosaminoglycan present in AM/UC tissue and has been demonstrated to play an important role in tissue morphogenesis and healing, imparting the anti-inflammatory and anti-scarring actions observed in AM clinically.⁷⁻⁹ In AM/UC, HMW HA has been shown to be covalently linked to the heavy chain-1 (HC1) of inter-alpha-inhibitor, forming the HC-HA complex.⁹ Studies have demonstrated that the HC-HA complex present in cryopreserved AM/UC acts by inhibiting pro-inflammatory cell adhesion, spreading, and proliferation, and by decreasing fibroblast proliferation and limiting the differentiation of fibroblasts into myofibroblasts, thus limiting the development of scar tissue.¹⁰⁻¹² Furthermore, cryopreserved AM matrix has been successfully used for minimizing postoperative inflammation, pain, and adhesion formations following various soft tissue reconstructive procedures, particularly in ophthalmology and plastic and reconstructive surgery.^{13,14}

When c-HAM matrix is used as a temporary patch in ophthalmology, neutrophils and macrophages rapidly undergo apoptosis, modulating the inflammatory response and promoting a more regenerative healing response.^{13,15,16} The use of AM in the treatment of burns is well documented, and demonstrated benefits include reduced pain, reduced mean time to epithelialization, less scar tissue formation, and fewer dressing changes and infection rates.¹⁷⁻²¹ Multiple studies have shown superior wound healing following the application of cHAM in chronic leg ulcers of varying etiology.²²⁻²⁴ Tendon and nerve wraps using AM in animal models led to decreased adhesion formation and improved functional outcomes.²⁵⁻²⁸ This data suggest the properties of AM and UC would be beneficial in surgery of the musculoskeletal tissue; this is particularly true for revision procedures.

The primary aim of this study was to compare preoperative with postopera-

tive outcomes of patients undergoing foot and ankle revisions and/or complex reconstructions with tendon and/or nerve involvement using amniotic membrane. We hypothesize that the use of cHAM/UC would be an effective adjunct treatment leading to reduced pain and improved functional outcomes in complex foot and ankle surgeries.

MATERIALS AND METHODS

We analyzed a retrospective case series of complex foot and ankle reconstructions and/or revision procedures in which CLARIX[®] CORD 1K (cHAM/UC, Amniox Medical, Inc., Atlanta, GA) was applied to the surgical sites in an attempt to improve outcomes. Inclusion criteria for this retrospective case series consisted of adult patients having undergone open foot and ankle surgical repairs with adjunctive use of cHAM/UC for the treatment of a variety of conditions in which there was tendon and/or nerve involvement. All patients failed a course of nonoperative therapy, which consisted of rest, activity modification, trial of durable medical equipment, physical therapy, and oral and/or topical analgesics. Nine of the 14 patients failed previous surgical management and required revisions and/or additional surgical repair. All patients had an injury history with tendon, nerve, or ligament damage. Exclusion criteria included patients without tendon or nerve injury, with less than one month of clinical follow-up and without a documented preoperative subjective pain assessment. We did not exclude any patients on worker's compensation insurance plans or who used tobacco. Fourteen patients (6 male and 8 female) underwent open foot and ankle surgery under the care of the senior author (MW) during the study period. All patients were available for follow-up within one month and met the inclusion criteria. Patient medical records were reviewed for all patients included in this study, and short-term follow-up results were analyzed as far out as one year.

The patient's age, sex, intraoperative findings, complications, and follow-up time were documented. The American Orthopedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale was completed preoperatively during the

patient's last clinic visit before surgery and at follow-up. The AOFAS Ankle-Hindfoot Scale is a foot- and ankle-specific clinical rating scale that combines a patient's subjective reporting of his or her pain and functional status, as well as the surgeon's physical exam. The scale is scored with a possible 100 points and is the most commonly used ankle survey.²⁹ The score is heavily weighted toward the patient's rating of his or her pain and function levels, representing 60 of 100 possible points. The patients' records were also reviewed with regard to the pain numeric rating scale (NRS), an easily administered, widely used, and validated measure of pain intensity.³⁰ The NRS asks patients to rate their current pain from 0 ("no pain") to 10 ("worst possible pain").

A paired *t* test was used for statistical comparison (GraphPad Prism 6, GraphPad Software, Inc., La Jolla, CA) of the AOFAS Ankle-Hindfoot Scale and pain NRS outcome measurements and assigned a *p* value. A *p* value $\leq .05$ was considered a statistically significant outcome. Percent change (preoperative versus postoperative) in the NRS was also assessed for those patients for whom this data was available (11 of the 14 patients).

RESULTS

The mean age at the time of surgery was 40 years (range, 22–81 years). The mean follow-up time was 15 weeks (range, 4–32 weeks). All 14 patients included in this cohort reported improvement, namely, lessened pain intensity both on the AOFAS Ankle-Hindfoot Scale and the pain NRS (Table I).

The mean AOFAS score improved from 50 (range, 17–79) preoperatively to 85 (range, 67–100) postoperatively. The mean NRS score also improved from 8 (range, 4–10 out of 10) preoperatively to 2 (range, 0–6 out of 10) postoperatively. Both outcome scoring systems showed statistically significant differences ($p < .0001$), when we compared the preoperative and postoperative results. All patients included in the cohort showed improvement in both outcome measures. The mean percent change in the NRS was 78% (range, 17%–100%).

Four patients experienced a postop-

TABLE I
Patient demographics and postoperative outcomes^a

Age, y	Sex	Procedure	Preoperative AOFAS Score	Postoperative AOFAS Score	AOFAS Score Gain, Preoperative v Postoperative	Follow-up, wk	Pain NRS Preoperative (0–10)/ Postoperative (0–10)	Percent Change Pain NRS, %
81	M	Posterior tibial tenodesis, TN arthrodesis	33	85	+52	28	10/0	100
46	M	Lengthening of 1st MTP, MTP to cuneiform fusion	70	87	+17	20	8/6	25
33	F	Excision of CN and tarsal coalition, fat transfer and amnion allograft	17	67	+50	4	NA	NA
38	M	Bilateral excision of plantar fibroma	41	67	+26	8	NA	NA
20	M	Foot and ankle reconstruction, perineal tenolysis	26	83	+57	16	8/4	50
33	M	Lateral column lengthening, posterior tibial tendon repair, peroneal tenolysis	38	87	+49	16	9/0	100
51	F	MTP arthroplasty, Akins osteotomy	75	85	+10	24	4/0	100
33	F	ADM repair, cryopreserved amion allograft to plantar plate	60	81	+21	32	6/5	17
59	F	Cheilectomy, neurolysis	50	100	+50	4	9/0	100
33	F	Akins osteotomy	79	89	+10	20	8/1	88
29	M	Ankle revision, Broström procedure, peroneal tenolysis	53	73	+20	14	NA	NA
54	F	Excision of plantar fibroma	72	92	+20	8	7/0	100
22	F	Fibular plate HWR, superficial peroneal neurolysis, peroneal tenolysis	32	98	+66	8	4/0	100
32	F	Excision of ganglion cyst	60	90	+30	8	10/2	80

^aAOFAS, American Orthopedic Foot and Ankle Society; NRS, numeric rating scale; TN, talonavicular; MTP, metatarsophalangeal; CN, calcaneonavicular; ADM, abductor digiti minimi; HWR, hardware removal

erative complication (29%). This included two cases of postoperative infection (one with a non-reabsorbed suture), which required subsequent localized debridement and washout of the surgical incision sites. Another patient experienced delayed bone union, which resolved within 2 months after a course of ultrasound bone stimulation. The fourth patient required 6 months of oral rivaroxaban anticoagulation treatment for a small, symptomatic, deep vein thrombosis. There were no complications directly related to the utilization of the cryopreserved amniotic membrane/umbilical cord.

DISCUSSION

The results of this retrospective review show that adjunctive use of cryopreserved amniotic membrane and umbilical cord in a variety of foot and ankle surgeries with tendon and/or nerve pathology is both safe and effective. Furthermore, the results demonstrate statistically improved patient assessments of both pain and functional status, a meaningful indicator that patients with existing foot and ankle pathology were able to resume daily and recreational activities without limitations and mostly, or completely, free of pain. The cohort included in this study was purposefully broad so as to include a variety of foot and ankle pathologies, with surgical intervention necessary to correct tendon, nerve, and/or bony abnormalities. This allowed for an assessment of the utility of amniotic membrane as an adjunct in tenorrhaphy and neuroorrhaphy.

Although a control group was not available for comparison in this study, postoperative outcome measures were comparable to those previously published,^{31–34} Bare and Ferkel reported a mean AOFAS score of 92 with a range of 68 to 100 for 30 repairs of peroneal tendons with arthroscopy.³¹ Redfern and Myerson reported a mean of 82 with a range of 20 to 100 for 28 open repairs without arthroscopy.³² More than half of the patients included in this study had a history of previous foot and ankle surgeries, and several patients had a history of multiple surgeries, whereas the current literature comments almost exclusively on those patients with primary repairs only. Additionally, nearly

this entire cohort presented with multiple overlapping etiologies, including chronic pain syndromes, requiring more than one surgical intervention. This cohort also included patients on worker's compensation insurance; such patients are known to have relatively poor outcomes in general. These distinct differences, when compared with the indications for surgery in much of the literature, may account for the lower mean preoperative AOFAS score in our study, 50; Bare and Ferkel reported a mean preoperative AOFAS score of 63.³¹

To our knowledge, this is the first case series to report outcome measures for tendon and/or nerve repairs in complex reconstructive and/or revision foot and ankle surgery utilizing cryopreserved amniotic membrane. Multiple studies in several animal models including chickens, rabbits, and rats have demonstrated statistically significant reductions in scar tissue formation and adhesions, as well as improvements in functional recovery in tenorrhaphy and neuroorrhaphy with amniotic membrane encapsulation.^{25–27,35–37} Ozbölük et al. reported a statistically significant decrease in adhesion formation following flexor tendon repair in a rabbit model in the amniotic membrane treatment group versus the control group with tendon repair only.²⁵ He et al. found that the rate and quality of tendonization was superior to the control when standard tenorrhaphy included amniotic membrane wrapping.³⁵

There are several limitations to this study. This is a small case series studying a heterogeneous patient population and several different surgical interventions. It was performed retrospectively, and, consequently, postoperative pain NRS scores were unobtainable for several patients included in the study. This study does demonstrate the relative safety of this tissue allograft, however, with no complications attributed to the matrix itself. Although we are unable to definitively comment on the amount of improvement attributable to amniotic membrane/umbilical cord in our study, the statistically significant improvement in postoperative outcome measures of function (mean postoperative AOFAS score, 85) and significant improvement in pain (mean percent change NRS score, 78%) suggests that adjunctive use of cHAM/UC intraoperatively may improve the results of tendon and/or

nerve repair by decreasing adhesion and scar tissue formation.

CONCLUSION

In the present study, the use of cryopreserved amniotic membrane and umbilical cord tissue in foot and ankle surgeries with tendon and/or nerve pathologies was examined. In this 14 patient retrospective study, we found that the use of cHAM/UC is both safe and effective. There were no postoperative complications attributed to cHAM/UC use, and postoperative outcome measures of function and pain were significantly improved with cHAM/UC use. Overall, these positive results warrant further study and review of short- and long-term patient outcomes. **STI**

AUTHORS' DISCLOSURES

Dr. Warner is a consultant for Amnio Medical, Inc. Mr. Lasyone has no conflicts of interest to report.

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