

Successful treatment of painful chronic wounds with amniotic and umbilical cord tissue: A case series

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Abstract

Patients with chronic wounds may experience persistent, debilitating pain that cannot be adequately managed with analgesics and that negatively impacts their quality of life. In this case series, three painful chronic and ischemic wounds that were caused by polyarteritis nodosa vasculitis ($n = 1$) and peripheral arterial disease (PAD) ($n = 2$) were successfully treated with cryopreserved umbilical cord tissue and/or amniotic membrane and umbilical cord particulate, resulting in notable reduction in pain within 7 days followed by expedited wound closure. No adverse events related to these tissue products were observed. These preliminary data demonstrate its safety and efficacy in reducing pain and promoting wound healing in painful chronic and ischemic wounds.

Keywords

Amniotic tissue, chronic wound, skin ulcer, umbilical cord, wound healing

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Introduction

Chronic wounds on the lower extremities are a major cause of morbidity and disability, affecting 1%–2% of the world's population and up to 5% of the elderly population.¹ These wounds are particularly difficult to treat and require constant medical attention, resulting in significant healthcare costs.² The healing process for a chronic wound can take 6–8 months,³ and some wounds last years or even decades.⁴ Living with a chronic wound has a large impact on the patient's quality of life,^{5–7} with pain being one of the symptoms that patients find particularly distressing.^{8–10} In fact, many patients find pain to be the worst aspect of ulceration, and at times consider pain relief to be more important than wound healing.^{11–13} The prevalence of pain with chronic wounds is 54%–87%,^{14–16} with up to 67% of patients reporting severe pain.¹⁴ Pain can further delay wound healing due to raised stress levels and compromised immune responses.¹⁷

The standard of care for chronic wounds entails debridement, pain management, dressing changes, and re-establishment of circulation, although these mechanisms have limited success in wound healing. Furthermore, opioids are commonly used to treat severe pain in chronic wound cases; however, they have a high abuse potential and limited alternatives.¹⁸ Thus, there is an unmet clinical need for a wound care treatment that aids in both pain control and wound

healing. Cryopreserved amniotic membrane (AM) and umbilical cord (UC) allograft tissue, which has been shown to promote wound closure in complex, non-healing foot ulcers,^{19–21} may be one potential solution. The therapeutic value of these tissues is derived from their anti-inflammatory and anti-scarring properties.²² These properties not only promote a regenerative environment to facilitate wound healing, but they may also alleviate nociceptive wound pain indirectly by reducing pro-inflammatory mediators.²³ Herein, we report the safe use of UC in promoting wound healing and pain alleviation in three cases with chronic and ischemic wounds. The clinical significance in managing the associated pain is further discussed.

Case presentation

Case 1

The patient is a 60-year-old African American female (body mass index (BMI): 29 kg/m²) with a long-standing history of

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Figure 1. Chronic painful vasculitic wound due to polyarteritis nodosa. (a) Painful wound on the left leg measured $6.7 \times 4.5 \times 0.1 \text{ cm}^3$ at initial presentation and was treated with negative pressure wound therapy (NPWT) and dressing changes. (b) At week 2, there was lack of epithelialization and pain was still severe (8–9/10), so umbilical cord (UC) allograft was applied. Pain resolved overnight (0/10), and the patient discontinued opioid use. NPWT was discontinued at week 3. (c) At week 4, a second UC graft was placed. (d) By week 11, progressive wound healing was evident along with remnant UC graft. (e) At week 12, an injection of 25 mg of AM/UC particulate was administered. (f) Complete wound closure with return of pigmentation was evident by week 19, following a second AM/UC particulate injection 2 weeks prior.

rheumatoid arthritis (RA) that was managed with methotrexate without success. She was eventually put on etanercept (Enbrel; Bristol Meyers Squibb, New York, NY) 1 year previously and developed painful lumps on her lower extremities that turned necrotic. The patient was subsequently placed on oral prednisone (20 mg per day); nonetheless, the RA remained “active” as demonstrated by high levels of rheumatoid factor and C-reactive protein. The patient is also a former smoker and suffers from non-diabetic peripheral neuropathy (treated with oral gabapentin (500 mg BID)) with numbness and paresthesia in the lower extremity (motor function: normal). The patient also suffers from hypertension and hypothyroidism managed with daily oral levothyroxine (0.1 mg daily).

The patient presented to the wound clinic with a chronic (>3.5 months) painful wound over the anterior tibia measuring $6.7 \times 4.5 \times 0.1 \text{ cm}^3$ on the left leg (Figure 1(a)). At presentation, the wound was thought to be caused by RA-associated vasculitis, etanercept-associated vasculitis, or polyarteritis nodosa. The diagnosis was confirmed to be polyarteritis nodosa about 2 months into treatment. The patient’s chief complaint was wound pain, which was being managed with 5–325 mg of oral oxycodone every 6 h. The

wound was tender to touch and had minimal non-viable tissue on the edges. The wound was initially treated with irrigation and curette-based debridement followed by application of lidocaine jelly to reduce pain. In addition, negative pressure wound therapy (NPWT) (KCI Medical, San Antonio, TX) with continuous -125 mmHg pressure was performed. Dressings were changed every third day under home care, and silver dressings (ACTICOAT 7; Smith & Nephew, Memphis, TN) were placed under the NPWT foam in contact with the wound. The patient returned to the clinic every 7 days.

Within the first 14 days, the wound had formed extreme exudate (Figure 1(b)), and the patient still suffered from severe pain, reporting an 8–9 out of 10 on the Numeric Rating Scale (NRS).²⁴ At this point, a piece of UC allograft (NEOX CORD; Amnio Medical, Miami, FL) was placed on the wound with non-adherent silicone dressing (Adaptic; Acelity, San Antonio, TX). Interestingly, the pain resolved overnight (score of 0/10 on the NRS), and she stopped taking opioids thereafter. At 3 weeks, the wound had drastically decreased in size with evidence of granulation, so NPWT was discontinued. At 4 weeks (Figure 1(c)), another UC allograft was placed on the wound. Over the next 7 weeks (Figure

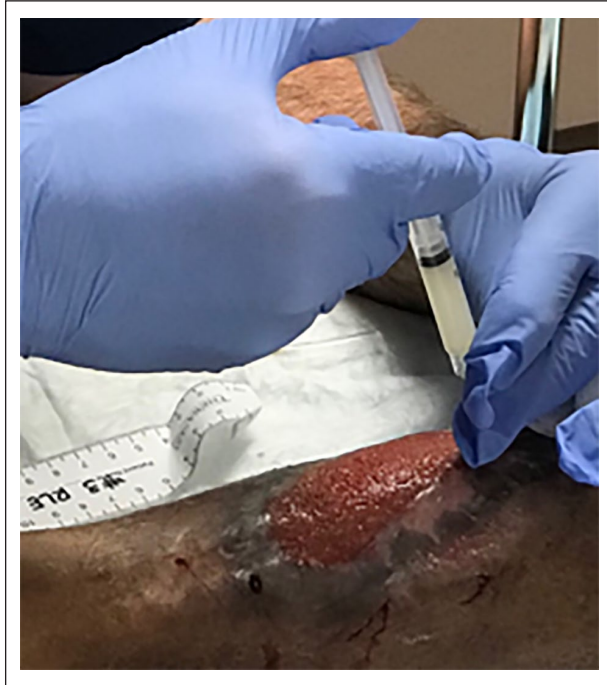


Figure 2. Representative example of AM/UC application. AM/UC particulate was reconstituted in preservative-free saline and injected around the wound parameter.

1(d)), the wound was covered by granulation tissue along with allograft remnant. At 12 weeks (Figure 1(e)), the wound measured $4.0 \times 2.0 \times 0.1 \text{ cm}^3$, and an injection of 25 mg of AM/UC particulate (NEOX FLO; Amnio Medical, Miami, FL) in 2 mL preservative-free saline was given (Figure 2), which resulted in reduction of the wound size and depth. At week 17, another AM/UC injection was administered, which ultimately resulted in complete wound healing 2 weeks later (Figure 1(f)). Upon healing, there was a return of pigmentation at the wound site without pain, scarring, or abnormal sensation. In summary, complete closure of a chronic painful and ischemic vasculitic wound was accomplished in 19 weeks with two UC allografts, two injections of AM/UC particulate, and NPWT for 3 weeks.

Case 2

The patient is a 66-year-old female (BMI: 21.5 kg/m^2) with a chronic full-thickness wound on the lateral, left extremity below the knee that developed after an arthropod bite 8 months prior. The patient has a medical history of hypertension, hyperlipidemia, depression, anxiety, and idiopathic neuropathy. The patient also has PAD and has undergone multiple procedures including percutaneous revascularization on the involved leg.

The patient complained of sharp pain localized near the wound that was being managed with 300-30 mg of oral acetaminophen-codeine as directed, 81 mg of oral aspirin

QD, and 20 mg of oral oxycodone as directed. Neurological examination revealed decreased sensation with the monofilament test. Physical examination revealed the initial wound measured $3.5 \times 2.4 \times 0.8 \text{ cm}^3$ with minimal non-viable tissue on the wound edge. The wound was initially treated with irrigation, 2% lidocaine spray, and debridement, followed by NPWT with a Sorbact® liner with continuous pressure of -125 mmHg and dressing changes every third day. One week later, the wound size decreased to $3 \times 1.5 \times 0.3 \text{ cm}^3$. At 2 weeks, the wound slightly decreased to $2.8 \times 1.4 \times 0.3 \text{ cm}$ (Figure 3(a)), and a $3 \times 2 \text{ cm}^2$ UC allograft (NEOX CORD) was placed over the wound with non-adherent silicone dressing (Adaptic). One week later (Figure 3(b)), the allograft remained over the wound bed, and the patient reported no wound pain (score of 0/10 on the NRS). Intense granulation tissue was seen by week 5 (Figure 3(c)), followed by closure of the wound by week 7 (Figure 3(d)).

Case 3

The patient is an 83-year-old female (BMI: 28.9 kg/m^2) with a chronic (>5 months) wound on the proximal, lower right leg following surgical excision of skin carcinoma. After excision, only dressings were applied, and the patient was told the wound would heal on its own. The patient has a medical history of insulin-dependent diabetes mellitus, hypertension, varicose veins, former smoker, arthritis, osteoporosis, and diabetic neuropathy. The patient also had previous triple bypass surgery and radiofrequency ablation to the heart.

Physical examination of the neck revealed bilateral carotid bruits. The patient also had faint femoral pulses, and both feet were cold to touch with prolonged capillary filling. Additional work-up suggested that the patient had severe carotid artery disease and PAD. A wound ($1.0 \times 1.2 \times 0.1 \text{ cm}^3$) was located on the proximal part of the right leg and diagnosed as an arterial ulcer (Figure 4(a)). The patient also complained of pain localized near the wound. Curette debridement was performed on the wound after topical application of 2% lidocaine gel. Medihoney (Derma Sciences, Toronto, Canada) and Mepilex Ag antimicrobial foam dressing were applied and changed weekly. The wound demonstrated healing at week 2 (Figure 4(b)) and week 3 (Figure 4(c)). At week 4, a $2 \times 2 \text{ cm}^2$ UC allograft (NEOX CORD 1K) was applied. Pain decreased to 0/10 on the NRS within 3 days, and the allograft remnant was still present 1 week later. Complete wound closure was achieved at week 6 (Figure 4(d)).

Discussion

Herein, we presented three patients with painful chronic and ischemic wounds that were caused by polyarteritis nodosa vasculitis ($n=1$) and/or PAD ($n=2$). All three patients complained of severe, localized wound pain that was managed with pain medication, including opioids in two cases. After

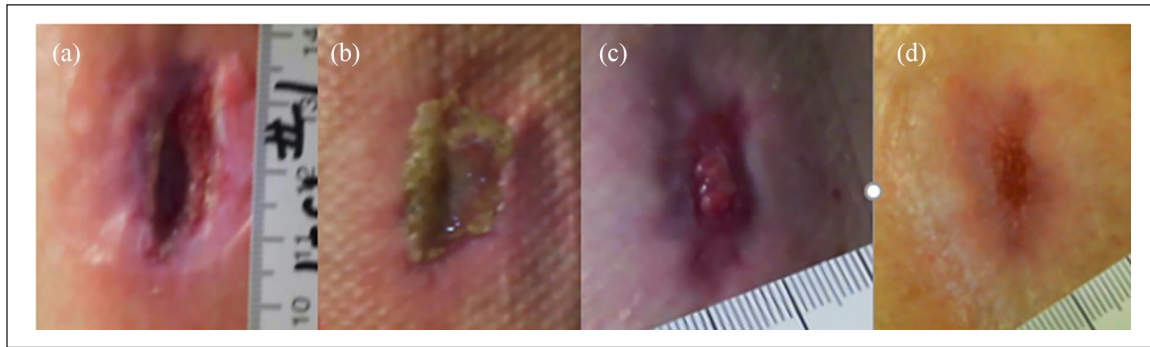


Figure 3. Chronic painful wound healing associated with PAD. (a) Umbilical cord allograft was applied to the wound at week 2. Progressive wound healing was seen thereafter at (b) week 3, (c) week 5, and (d) week 7.

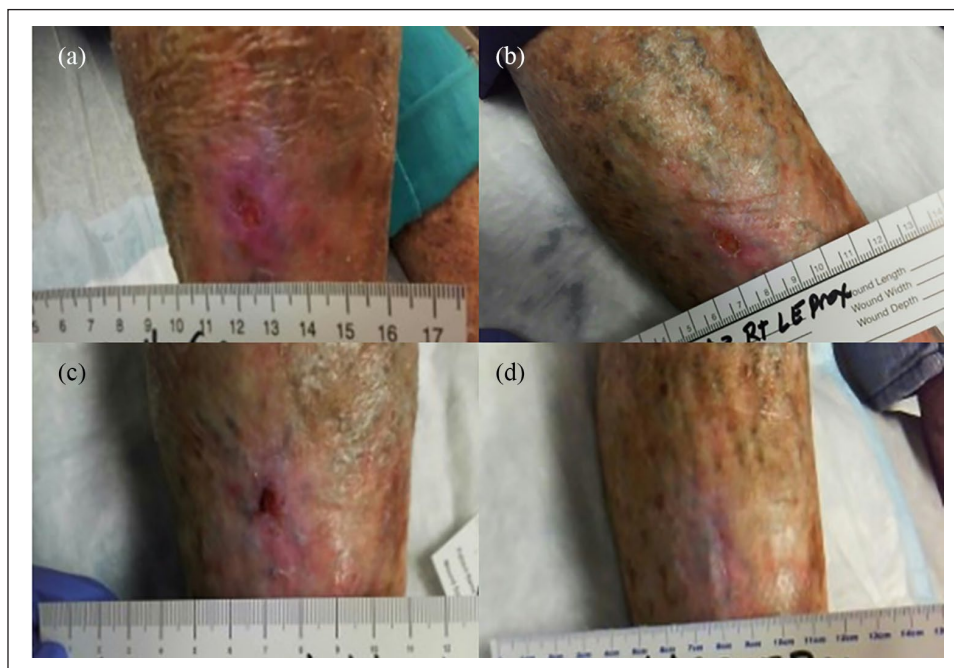


Figure 4. Chronic painful arterial wound. (a) Initial wound was treated with honey gel and antimicrobial foam dressing. Wound showing healing at (b) week 2 and (c) week 3. (c) Umbilical cord allograft was applied at week 4, and wound pain resolved 3 days later. (d) Complete wound closure was seen at week 6.

treatment with UC allograft in all three patients and injection of AM/UC particulate in one patient, we observed rapid reduction of pain followed by wound closure. There were no adverse events related to the AM/UC used.

The pain associated with chronic wounds is often debilitating, and consequently can limit daily activities, disrupt sleep, and affect quality of life.^{25,26} In 40%–57% of these cases, opioids are routinely administered to manage wound pain.²⁷ However, opioid exposure is associated with reduced wound healing due to altered keratinocyte biology²⁸ and insufficient pain relief in many patients.²⁹ In addition, opioids are associated with harmful side effects (such as drowsiness, dizziness, nausea, vomiting, and constipation),³⁰ have a high abuse potential, and are notoriously associated with overdose and death.¹⁸ In this case

series, patients had pain alleviation within 1–7 days after application of UC allograft, and the two patients discontinued use of opioids. The former is consistent with a case series of cervical necrotizing fasciitis that reported absence of pain 4 days after debridement and AM application.³¹ Burn patients have also reported significantly less pain on days 1–4 of AM application, further supporting the ability of AM to rapidly relieve wound pain.³² Several studies have also reported significantly less analgesic or narcotic usage in patients treated with AM following penile implant procedures³³ and cesarean section,³⁴ supporting the notion that AM may also be useful in reducing opiate usage.

Nociceptive pain is caused by inflammatory mediators in the wound micro-environment in response to tissue damage. Inflammatory responses following tissue damage sensitize

peripheral nociceptors in the skin,³³ and this inflammatory response is often prolonged in chronic wounds as demonstrated by elevated levels of cytokines (e.g. tumor necrosis factor α (TNF- α), interleukin 1 (IL-1), transforming growth factor β (TGF- β)), proteases, and matrix metalloproteinases (MMPs).^{34–36} The presence of wound infection further stimulates inflammatory responses and neutrophil infiltration, which can exacerbate pain levels experienced.³⁷ Other sources of wound pain could be friction/shear, moisture-related damage, nerve damage, blood vessel injury, and ischemia which leads to hypoxia and can increase infection rates.³⁸ To manage wound pain, the underlying nature of the patient's pain must be assessed. For example, changes in body position and movement are beneficial for predictable pain. Dressings with non-aggressive adhesives and moisture control are important to provide an appropriate physical environment for healing.³⁹

AM tissue has been shown to improve burn and wound-related pain and increase patient tolerance during wound dressing changes.^{31,32,40,41} Several prospective, randomized controlled trials have also shown that AM significantly reduces post-operative pain and can even lower analgesic usage as soon as 24 h post-op.^{42–44} AM and UC are also valuable in especially providing biological factors to accelerate the healing process by managing the cellular and molecular environment. AM and UC have been shown to promote apoptosis and phagocytosis of neutrophils while reducing secretion of inflammatory cytokines.^{23,45,46} In addition, AM and UC tissues have been shown to suppress TGF- β signaling, which directly suppresses scar formation and favors keratinocyte proliferation and migration.^{35,47–49} The presence of neuropeptides within the UC tissue may also modulate the function of immunocompetent and inflammatory cells to promote cutaneous innervation that is vital for successful wound healing.⁵⁰ Based on the pathophysiology of the wounds with background pain³⁹ presented in this case series, the aforementioned properties are likely responsible for the notable reduction in wound pain following AM/UC application and promote an adequate environment for wound healing. Overall, these cases suggest AM and UC may be a safe treatment option in reducing wound pain and promoting closure of chronic and ischemic wounds.

Conclusion

This case series highlights the utilization of AM and UC tissue to rapidly alleviate pain and promote closure in painful chronic and ischemic wounds. Pain reduction may be an early clinical surrogate of successful wound healing that physicians should monitor in their patients.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series

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Informed consent

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