Scientific Research Publishing

Surgical Science, 2021, 12, 76-94
https://www.scirp.org/journal/ss
ISSN Online: 2157-9415
ISSN Print: 2157-9407

Complex Limb Salvage with Placental-Based Allografts: A Pilot Study

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How to cite this paper: Thornburg, D.A., Kowal-Vern, A., Tettelbach, W.H., Foster, K.N. and Matthews, M.R. (2021) Complex Limb Salvage with Placental-Based Allografts: A Pilot Study. *Surgical Science*, **12**, 76-94.
https://doi.org/10.4236/ss.2021.123010

Received: February 12, 2021
Accepted: March 19, 2021
Published: March 22, 2021

Abstract

Background: Commercially available human placental amnion/chorion tissue allografts have been successfully used as protective treatment barriers for wounds and diabetic ulcers. Burn and traumatic limb injuries with exposed bone or tendon generally require surgical flaps or amputations for healing. The purpose of this study was to determine if dehydrated human amnion/chorion membrane allografts (dHACM) with decellularized human collagen matrix (dHCM) could be used to salvage injured human extremities. **Methods and Materials:** dHACM/dHCM was topically applied to the wounds after debridement. Negative Pressure Wound Therapy (NPWT) was concurrently initiated, primarily to bolster the tissue with moisture and contamination control. Approximately every seven days, wounds were re-evaluated for granulation tissue growth response. As needed, patients received dHACM/dHCM and NPWT in the outpatient or home care settings after discharge. **Results:** Fifteen males and two females (26 extremities) were treated for fourteen burn and three Necrotizing Soft Tissue Infections (NSTI) injuries. Closure was observed in patients after two to five dHACM/dHCM applications. The dHACM/dHCM treatment was initiated: (median) 17-days after injury; NPWT for 17-days; autograft or primary closure after 21-days; discharge 25-days after the first application. **Conclusion:** Treatment with human placental-derived allografts provided a protective covering that enabled the healing cascade to generate granulation tissue formation in extremity wounds with exposed tendon and/or bone. In select limb salvage cases, dHACM/dHCM treatment may be a promising alternative to amputations,

tissue rearrangements, free tissue flaps or other techniques for resolution of extremity wounds with bone and tendon exposure.

Keywords

Burns, Trauma, Placental Tissue, Amnion, Chorion, Burns, Necrotizing Soft Tissue Infections (NSTI)

1. Introduction

The most common interventions to heal burn and traumatic limb injuries with exposed bones and tendons include skin graft coverage, local or microvascular flaps, as well as amputations [1] [2]. Antecedent to limb removal, surgeons follow the reconstructive ladder for management of complex wounds with the following strategies: closure by primary or secondary intention, delayed primary closure, skin grafts, tissue expansion, local tissue rearrangement, and autologous tissue transfer-flaps [3] [4].

Placental amniotic membrane has been used as a wound dressing for more than 100 years [5] [6]. Currently, an additional modality has been added to the armamentarium of limb wound closure to prevent amputations. Technology has revolutionized the development of biological wound dressings for clinical use [7] [8] [9] [10] [11]. Dehydrated human amnion/chorion membrane allograft (dHACM), (MiMedx Group Inc., Marietta, GA) has been used to aid in wound closure, diabetic foot ulcers, partial and full thickness burns, donor sites, and surgically debrided areas [12]-[17]. Placental-derived allograft barriers or dressings, such as dHACM and decellularized human collagen matrix (dHCM), (MiMedx Group, Inc., Marietta, GA), also provide a protective environment which can support granulation tissue formation as well as supply a connective tissue matrix, respectively.

In utero, native human amnion/chorion membranes contain an array of factors, which play critical roles in regulating tissue development and growth. Epidermal Growth Factor (EGF), basic fibroblast growth factor (bFGF), Keratinocyte Growth Factor (KGF), Transforming Growth Factor alpha and beta (TGF-α and TGF-β), Vascular Endothelial Growth Factor (VEGF) and Tissue Inhibitors of Metalloproteinases (TIMPs) are some of the regulatory proteins that have essential roles in physiological processes required for healthy tissue generation, such as cell migration, proliferation and recruitment [10] [18] [19]. The purpose of this study was to determine if dHACM applied in tandem with dHCM (dHACM/ dHCM) could be used to aid in the salvage of extremities at high risk for amputation due to burns, trauma or Necrotizing Soft Tissue Infections (NSTI).

2. Methods and Materials

2.1. Sample Population

This observational retrospective pilot study performed from January 2019 through

October 2020 was approved by the Institutional Review Board for human studies. The inclusion criteria for treatment with dHACM/dHCM were: 1) exposed bone or tendon; 2) burn, trauma, or NSTI injuries; 3) failed split thickness skin graft (STSG) applications; 4) inadequate production of granulation tissue. The exclusion criteria were: 1) deep circumferential bone burn; 2) open joint; 3) continued tissue necrosis with tangential excisional debridement (TED) in the week after admission; 4) non-clearance of tissue infection with TED or antibiotics; 5) unstable lower limb ankle joint; 6) unrepairable peripheral vascular disease (no pulse or adequate arterial run-off to the feet).

2.2. dHACM and dHCM

The PURION® processed dHACM and dHCM are cleansed and dehydrated from donor-screened and tested elective caesarean section delivered placentas [7] [8] [9] [10] [11]. These placental-derived allografts undergo terminal sterilization to further reduce the possibility of an occurrence of a non-sterile unit. dHACM contains non-viable cells; dHCM is derived from the placental disc and contains mostly Type l human collagen. Both dHACM and dHCM contain over 250 identified regulatory proteins [7] [11]. In addition, dHACM and dHCM can be stored at room temperature for five years.

2.3. Treatment Process

Prior to placental-derived tissue application, burn or NSTI wounds were debrided of dead or necrotic tissue with the water knife Versajet II Hydrosurgical System (Smith + Nephew, Andover, MA) [20]. They were cleansed with normal saline and a stabilized hypochlorous acid solution. Bone trephination exposed bone capillaries and arterioles to promote granulation tissue generation over the wounds and avascular areas [1] [21] [22]. Negative pressure wound therapy (NPWT) via the ACTIV.A.C™. Therapy system (3M Corporation, San Antonio, TX) was applied at 125 mmHg to promote cleansing, limit bacteria, stimulate granulation tissue growth, and increase wound bed vascularity [23].

Once the injured area was prepared, dHACM/dHCM were topically applied or packed (depending on wound depth), covered with either a nonadherent dressing, 3% bismuth tribromophenate petrolatum dressing, or a glycerol-hydroxyethylcellulose lubricant, and bolstered with NPWT at 50 - 100 mmHg (**Figures 1-5**). The wounds were re-evaluated every seven days for granulation tissue formation after removal of the NPWT device and underlying dressing. The wound bed was appropriately debrided and dHACM/dHCM were reapplied over or into the wound, if required. dHACM/dHCM treatment was continued until bone, tendon and muscle were covered with adequate granulation tissue to sustain a Split Thickness Skin Graft (STSG). Skin grafts were bolstered under a NPWT device to minimize shear effect and sub-graft fluid accumulation, which could potentially damage or lift the graft off the wound bed and disrupt the intracellular signals critical for successful graft incorporation [24] [25] [26]. This practice

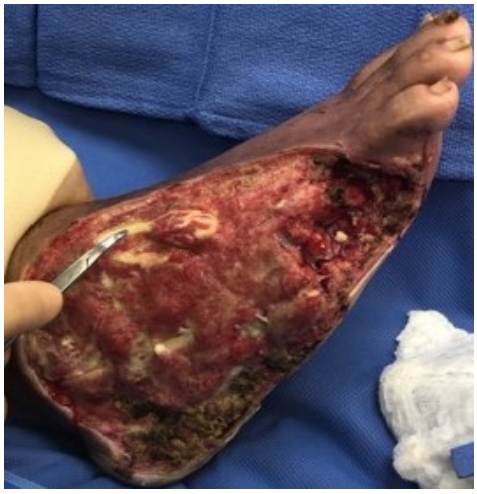

Figure 1. Transfer with contact burn wound (25-day-old wound with little toe amputation).

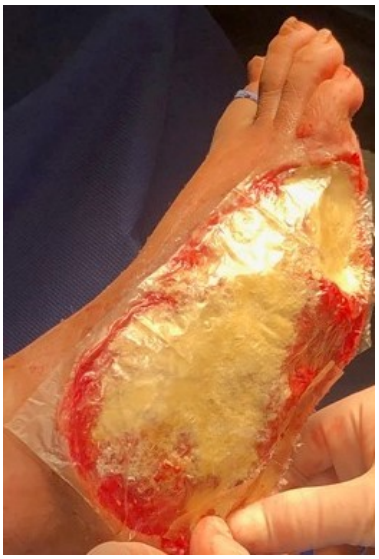

Figure 2. Additional application of dHACM/dHCM over granulation tissue formation on the wound.

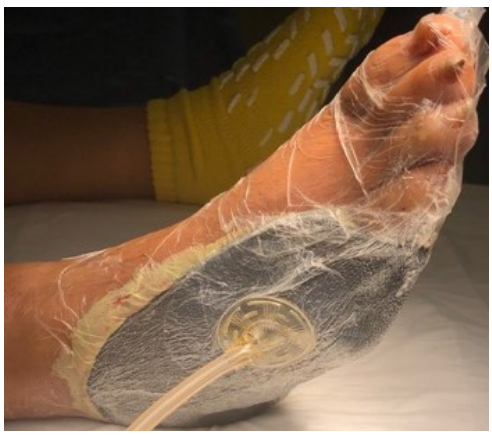

Figure 3. NPWT application over the healing wound.

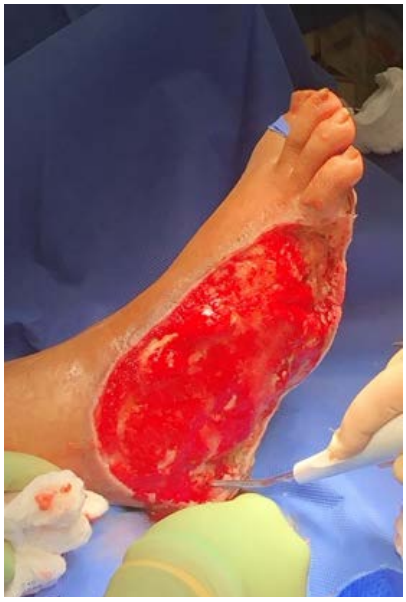

Figure 4. Healthier granulation tissue bed now evident once all dressing removed prior to split thickness skin grafting.

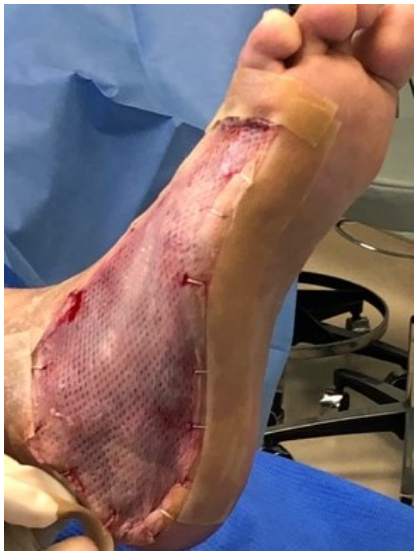

Figure 5. Split thickness skin graft application over wound granulation tissue.

was adopted in limb salvage protocols to fortify allografts such as dHACM and dHCM. To minimize disturbances to the protected wound healing environment, NPWT dressings were changed once a week instead of the usual wound care strategy of two-three times a week.

2.4. Statistical Analysis

Statistical analysis was performed with Statistica® (StatSoft, Tulsa, OK): descriptive statistics, one way-ANOVA, with unequal N Tukey post-hoc comparisons, and Maximum Likelihood chi-squared tests. Comparisons were made between the patients with leg, foot, combined leg and foot, and upper extremity injuries.

One-way ANOVA and Tukey statistics compared the following: age, percent total body surface (%TBSA), body mass index (BMI), operating room (OR) visits, extent of tangential debridement, autograft areas, length of stay (LOS), time to application of the dHACM/dHCM, time from application to autograft, time from first application to discharge, duration of NPWT use during treatment with these dressings, number of surgeries, and OR visits. Maximum Likelihood chi-squared compared ethnicity, gender, injury location, mechanism of injury, discharge location, comorbidities (diabetes, hypertension, cardiac, renal, etc.), alcohol/drug use, and infection. In all cases, a $p < 0.05$ value was considered significant.

3. Results

Table 1 depicts the demographic characteristics of patients with tendon and bone exposure after burn injury (14 patients, 82%) and necrotizing fasciitis (3 patients, 18%). There were seventeen patients with 26 extremities: 11 legs, 13 feet, two upper extremities. The mean ± standard deviation (median) age was 48.8 ± 16.5 (48) years; % TBSA, 3.3 ± 4.0 (1.3); and length of hospital stay 43.4 ± 20.7 (39) days. Ethnicity consisted of the following: seven (41%) each for White and Hispanic/Latino patients, two (12%) Black, and one (5.9%) Native American Indian. The major co-morbidities were diabetes, hypertension and cardiovascular disease. Admission laboratory values showed the following median, interquartile range (IQR): C-reactive protein, 92 (39 - 225) mg/dl; glucose, 167 (114 - 218) mg/dl; pre-albumin, 11.0 (8 - 18) mg/dl; transferrin, 166 (129 - 214) mg/dl; and hemoglobin A1c, 7.4 (6.9 - 10.2)%. Patients with both leg and foot involvement had a higher %TBSA, ($p = 0.02$) and a longer LOS than those with only foot involvement, ($p = 0.035$). In addition to burns on other anatomical locations, two patients had upper extremity wounds, which received dHACM/dHCM, and closure occurred.

Table 2 shows the dHACM/dHCM treatment process duration. Wound bed preparation lasted a median of 25-days from injury or admission. The median time interval from the start of dHACM/dHCM application to autograft placement was 25-days, and from the first application to discharge 26-days. The combined United States dollar ($USD) cost for only the dHACM/dHCM products was (median, IQR) of $15,410 ($10,940 - $21,440), as shown in Table 3.

Table 1. Demographic characteristics of patients receiving dHACM and dHCM.

	Leg	Foot	Leg-Foot
Patients	6 (35)	8 (47)	2 (12)
Extremities	9 (35)	11 (42)	2 & 2 (23)
Age (years)	57.3 ± 20.7 (59)	45.5 ± 8.7 (46)	51.0 ± 15.6 (51)
White	2 (29)	4 (57)	1 (14)
Hispanic/Latino	3 (43)	4 (57)	0

Continued

Black[†]	1 (50)	0	0
Native American Indian	0	0	1 (100)
LOS (days)	56.5 ± 19.7 (55)	29.6 ± 10.8 (34)	77.0 ± 1.4 (77)
Male/female	5/1	7/1	2/0
Number of admissions	1.8 ± 1.0 (1.5)	2 ± 1 (2)	1 ± 0 (1)
%TBSA	3.7 ± 2.6 (3)	1.0 ± 0.3 (1)	10.0 ± 5.7 (10)
BMI (kg/m^2) $^+p = 0.003$	$^+$23.3 ± 2.9 (23)	$^+$32.5 ± 4.5 (32)	26.4 ± 0.8 (26)
Burn injury[††]	5 (33)	6 (40)	2 (13)
NSTI	1 (33)	2 (67)	0
Admission gangrene	1 (25)	3 (75)	0
Diabetes $p = 0.038$	2 (18)	7 (64)	2 (18)
Cardiac	3 (43)	3 (43)	1 (14)
Hypertension	3 (38)	5 (62)	0
DVT	1 (25)	3 (75)	0
PVD	1 (100)	0	0
Renal	2 (40)	2 (40)	1 (20)
Alcohol + Drugs	4 (50)	1 (13)	1 (12)
Discharge home	1 (13)	7 (88)	0
Discharge SNF	5 (62)	1 (13)	2 (25)
Homeless	2 (33)	1 (67)	0

Mean ± standard deviation (median); Number (percent) = # (%); dHACM = dehydrated human amnion-chorion membrane; dHCM = decellularized human collagen matrix; total body surface area (TBSA); length of stay = LOS; BMI = body mass index; NSTI = necrotizing soft tissue infections (these three cases had necrotizing fasciitis); [††]two (13%) additional burn injuries (hand and forearm); DVT = deep vein thrombosis; PVD = peripheral vein disease; SNF = skilled nursing facility; two male patients had 1% TBSA hand-forearm full thickness burn injuries in addition to their leg-foot involvement; their combined age was 29.5 ± 14.8 (30) years. [†]The Black patient, who died with a total 95% TBSA, also had a hand/forearm burn.

Table 2. dHACM and dHCM treatment timeline.

	Leg	Foot	Leg & Foot	Hand/Forearm	Combined
Total surgeries	8.3 ± 1.8 (9)	7.4 ± 1.6 (8)	13.0 ± 2.8 (11)	2 ± 0 (2)	7.8 ± 3.0 (8)
OR TED (#)	8.0 ± 2.6 (9)	6.6 ± 1.1 (6)	12.5 ± 0.7 (13)	--	7.8 ± 2.5 (7)
Tissue debrided (cm^2)	388.3 ± 262.6 (425)	153.8 ± 100.9 (140)	600.0 ± 424.3 (600)	133.0 ± 95.5 (133)	279.2 ± 248.7 (188)
Injury to admit (days)	13.7 ± 22.7 (4)	12.1 ± 14.3 (8)	2.5 ± 2.1 (3)	--	10.2 ± 16.2 (3)
Days to TX	43.5 ± 38.4 (34)	16.3 ± 8.3 (14)	19.0 ± 4.2 (19)	--	26.2 ± 25.8 (16)
TX to discharge (days)	26.7 ± 15.0 (25)	20.0 ± 12.2 (20)	58.0 ± 5.7 (58)	--	29.3 ± 18.8 (26)
TX to STSG (days)	20.2 ± 16.9 (14)	28.7 ± 17.6 (23)	37.5 ± 6.4 (38)	--	27.3 ± 15.4 (25)
NPWT (days)	17.8 ± 9.5 (18)	16.9 ± 8.0 (15)	36.5 ± 7.8 (37)	14.0 ± 0 (14)	19.9 ± 10.5 (14)
Autograft (cm^2)	399.0 ± 250.8 (350)	90.0 ± 61.2 (83)	1025 ± 601.0 (1025)	150.0 ± 70.0 (150)	325.7 ± 381.4 (200)

Mean ± standard deviation (median); dHACM = dehydrated human amnion-chorion membrane; dHCM = decellularized human collagen matrix; TX = treatment with dHACM/dHCM; STSG = split thickness skin graft; OR TED = operating room tangential excision debridement; Leg & Feet versus Feet in OR TED $p = 0.029$; Leg & Foot versus the Leg and the Foot: days TX to discharge $p = 0.0189$.

Table 3. dHACM and dHCM cost summary.

	Leg	Foot	Leg-Foot	Upper Extremity	Combined
dHACM*	5866 ± 4634	13,204 ± 7847	127,3778 ± 50,491	6840 ± 0	23,298 ± 41,660
cost $USD	(4518)	(13,240)	(127,378)	(6840)	(8090)
dHCM**	5167 ± 4810	6675 ± 2844	27,700 ± 4384	4100 ± 0	8222 ± 7894
cost $USD	(3100)	(6200)	(27,700)	(4100)	(5150)
dHACM/dHCM	11,033 ± 7963	18,479 ± 8146	142,778 ± 34,510	10,940 ± 0	28,970 ± 42,935
Total cost $USD	(8668)	(18,610)	(142,778)	(10,940)	(15,410)

Mean ± standard deviation (median); $USD= $ United States dollar; *dHACM = dehydrated human amnion/chorion membrane, (MiMedx Group Inc., Marietta, GA); **dHCM = decellularized human collagen matrix, (MiMedx Group Inc., Marietta, GA).

3.1. Outcomes

Nine (53%) patients completed treatment in one admission, three (18%) were readmitted once, and five (29%) were readmitted twice for either autograft placement or infection. After treatment with dHACM/dHCM, thirteen patients received autografts, two underwent a delayed primary closure, and one had autografts and flaps to cover bilateral knee defects. Four (22%) of the patients had or required toe or partial foot amputations on admission due to gangrene or late presentation. Of two patients who failed the dHACM/dHCM treatment, one required a below knee amputation, and another had an infected foot wound on readmission that required a trans-metatarsal amputation. These two patients did not respond to treatment due to one or more of the following factors: poorly controlled diabetes, infection, and inadequate generation of granulation tissue. Eight (47%) patients underwent bone trephination in the wound area to stimulate granulation tissue development. Ten (59%) patients either presented with or developed an infection (cellulitis, septic shock) during the hospitalization. Seven patients had unsuccessful trials with a bilaminate sheet composed of cross-linked bovine tendon collagen and shark glycosaminoglycans (chondroitin-6-sulfate) with a silicone sheet cover, Integra®, (Integra Life Sciences, Princeton, NJ) prior to treatment with the placental-derived allograft dressings. One patient had a successful incorporation of the Integra® into the wound after dHACM/dHCM supported formation of adequate granulation tissue in the wound bed. Significantly more patients with foot salvage were discharged home compared to those with leg or leg and foot salvage, who were discharged to skilled nursing facilities, $p = 0.005$. There was one (5.9%) of seventeen patients who succumbed to a 95% TBSA flame burn after a 323-day hospitalization. Duration follow-up for thirteen of the seventeen patients was a median (IQR) of 438 (116 - 489) days with retained limbs and no complications. The four patients had no follow-up: two required amputations, one was lost to follow-up, and one died from the severe burn injury. Patients were seen "as needed" in clinic for one and a half years until the study ended in November 2020.

3.2. Case 1

A 79-year-old male was admitted to the burn center three days after sustaining a full thickness 2% total body surface area (TBSA) contact burn to his right lower

extremity (RLE) after falling on a space heater at home. His co-morbidities consisted of Type 2 diabetes (HbA1c = 7.2%), hypertension, dyslipidemia, dementia, and a history of a coronary artery bypass (CABG) surgery. His medications included aspirin and an antiplatelet medication. Evaluation of the injured extremity revealed peripheral vascular disease. During a bilateral lower extremity angiogram, a right popliteal artery atherectomy and balloon angioplasty were performed to improve blood flow. He had nine OR visits for tangential excisional debridement (400 cm^2) during an 89-day hospital stay. After two unsuccessful trials with Integra®, his treatment with dHACM/dHCM started on day 42 of hospitalization. Sixteen days after the initial application of dHACM/dHCM, his wound was autografted (**Figures 6-8**). In total, the patient received 350 cm^2 of dHACM and 2000 mg of dHCM at a combined product only cost of $17,780. He has not reported any issues or complications in follow-up for the past two years.

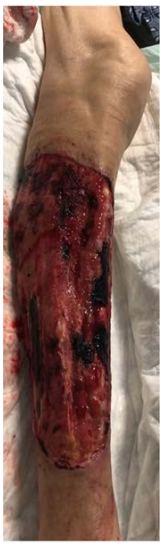

Figure 6. Right leg contact burn with exposed bone on admission.

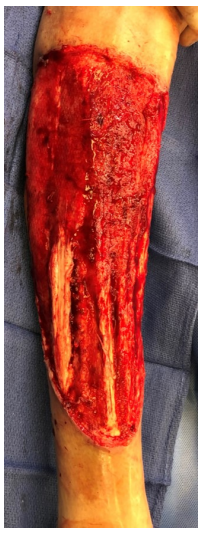

Figure 7. Exposed bone and tendon after debridement.

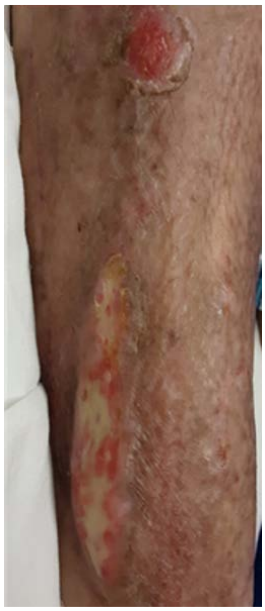

Figure 8. Day 122 after initial injury.

3.3. Case 2

A thirty-one-year-old male arrived in the emergency room with left lower (LLE) extremity pain, swelling, and fever. He was admitted to the medical intensive care unit for septic shock, NSTI, bacteremia, acute renal failure, and deep vein thrombosis of the affected leg. After transfer to the burn center, he underwent left leg fasciotomies for compartment syndrome, and six debridement procedures of the foot plantar surface to remove necrotic tissue and prepare the wound bed for closure (**Figure 9**, **Figure 10**). With intravenous antibiotics, appropriate renal treatment, and anticoagulation, the patient stabilized. During his 22-day hospitalization, his lateral and medial leg fasciotomies were closed using the DermaClose device (Synovis, Birmingham, AL), which is a continuous external

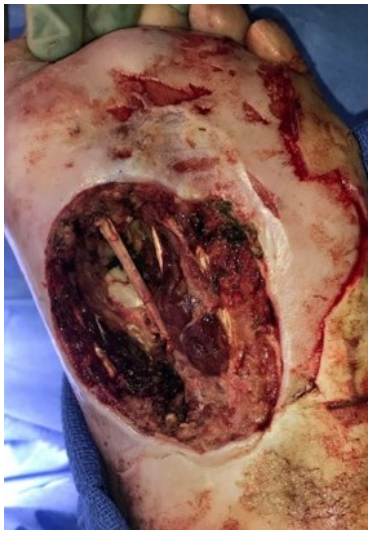

Figure 9. Debrided plantar wound on admission.

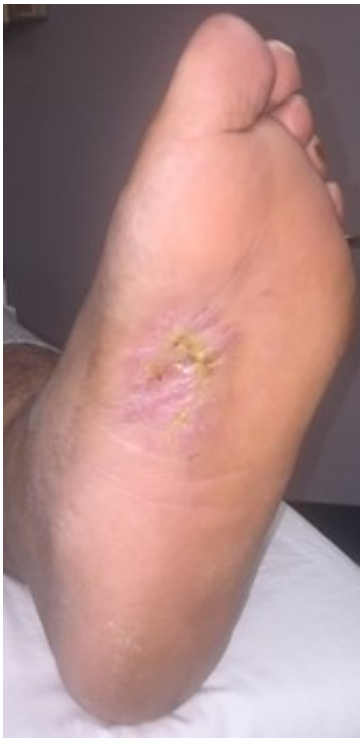

Figure 10. Healed scar during clinic visit.

tissue expander. The left foot plantar wound received dHACM/dHCM with bolstering NPWT set at 100 mmHg continuously, on the 13th day of his hospital stay. He had an additional one-day hospitalization for autografting of the plantar wound (50 cm^2). In total, he received 720 cm^2 of dHACM and 4000 mg of dHCM at a combined product only cost of $35,560. His follow-up at 328 days since injury has shown complete closure and no complications.

3.4. Case 3

A forty-year-old male was intubated on admission to the burn center after he was "found down" outside on the pavement during the summer months in South-Central Arizona. He was treated for fulminant diabetic ketoacidosis (admission glucose level 1053 mg/dl; HbA1c was 7.9%. He had 14% TBSA full thickness contact burns of his scalp, right upper extremity, and bilateral lower extremities. The burns on his legs, knees, and feet had exposed tendon and bone. His hospitalization was complicated by a myocardial infarction, electrolyte imbalances, and diabetic management. During his 78-day hospitalization, he underwent thirteen OR visits for multiple debridements (900 cm^2). A trial with Integra® was not successful. Treatment with dHACM/dHCM was started along with NPWT on the 16th day after injury. Thirty-three-days later the wound bed was sufficiently prepared to receive a 1450 cm^2 autograft (**Figures 11-14**). In total, he received 4479 cm^2 of dHACM and 13,000 mg of dHCM at a combined product only cost of $167,180. He achieved complete closure of all his wounds with no complications is currently walking with a cane.

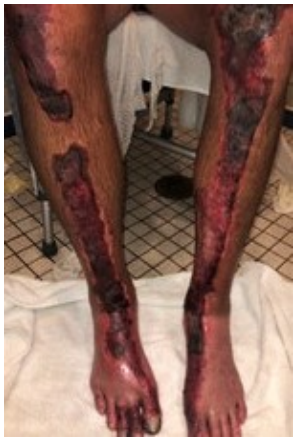

Figure 11. Debrided pavement contact burns (hospital day four).

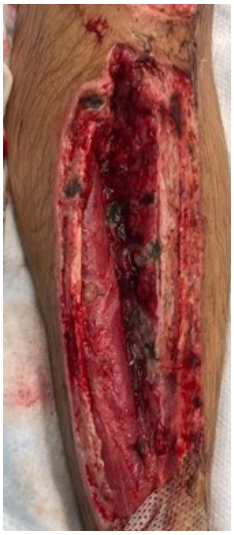

Figure 12. After debridement, thrombosed vessels with exposed bone/tendon.

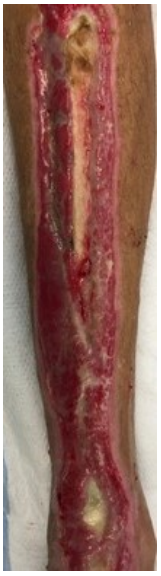

Figure 13. Granulation tissue formation starting to cover wound defect.

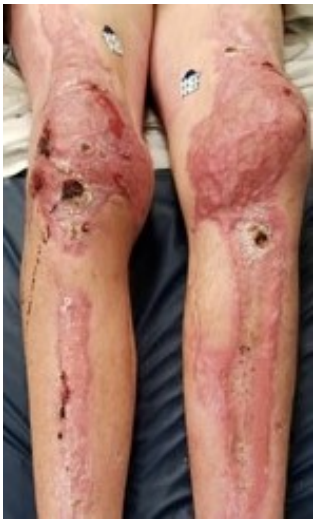

Figure 14. Treated with dHACM/dHCM and bilatral knee flaps.

4. Discussion

In this study, patients who received dHACM in tandem with dHCM as a barrier and placental-based connective tissue matrix, respectively, over exposed deep tissue structures demonstrated limb preservation in 24 of 26 (92%) extremities (eleven legs, twelve feet, and two hand and forearms). As expected, patients with both foot and leg involvement underwent more surgeries, received more dHACM/dHCM, required longer NPWT treatment duration, and had a longer LOS than single foot or leg injury patients. Although all patients included in this analysis were candidates for amputation, a limb preservation rate of 92% observed in this complex wound cohort should give providers pause to reevaluate current amputation protocols, and consider alternative pathways weighted towards limb salvage. **Table 4** lists the current literature where placental tissue was successfully used to cover exposed bone and tendon, and to support granulation tissue growth that is crucial to achieve limb salvage in this targeted study population.

While bone trephination promoted granulation tissue generation, adequate coverage of tendons was still an occasional problem. One solution might be to consider the injection of human placental-derived tissue into the culprit tendon as reported by Lei *et al.* [11]. When this approach was used, the treating provider observed a reduction in fibrous tissue formation in the injured tendons and ligaments as well as decreased inflammation, which may have been factors in the inhibition of granulation tissue adherence to the tendon surface [11].

In 2006, Parrett *et al.* reported that with autografts and flaps, seven of 40 (17.5%) limbs required amputations [1]. In this limb salvage study, there were two (8%) amputations after treatment with dHACM/dHCM due to one or more of the following factors: poorly controlled diabetes, infection, and inadequate granulation tissue generation. For wounds with exposed bone and tendons in patients with burns, trauma and infections, skin grafts and flaps have been the main deterrents to amputation. While many of these patients may not have been

Table 4. Literature reports on the use of placental membranes for exposed tendon/bone wounds.

Author	Year	Cases	Wound	Placental allografts
Sabella [5]	1913	5	4 burn, 1 trauma	amnion/chorion/umbilical cord, normal saline
Stern [6]	1913	12	11 burn (≤9 cm^2); 1 trauma	amnion/chorion; normal saline; petrolatum wax
Gruss [14]	1978	7	trauma	amnion/chorion; normal saline; 0.025% Na hypochlorite
Sheikh [27]	2013	4	trauma	dHACM*
Torabi [28]	2015	7	trauma	amnion/chorion; STSG
Frykberg [16]	2016	30	diabetic ulcers	viable cryopreserved human placental membrane (vCHPM)
Schlanser [22]	2018	1	trauma	mdHACM**
Current Study	2020	17	burn + NF	dHACM* and dHCM*

NF = necrotizing fasciitis; STSG = split thickness skin graft; * (MiMedx Group Inc., Marietta, GA); mdHACM** = micronized dHACM, (MiMedx, Marietta, GA).

ideally suited for flap reconstruction, they were candidates for dHACM and/or dHCM. The use of flaps for covering these wounds is important but has distinctive problems and complications [29]-[34]. Some of the flap complications may be partial or complete failure in the transfer, as well as wound congestion, full or partial flap necrosis, wound dehiscence, donor site deformity or morbidity such as loss of physical function with the use of muscle flaps [29]-[34]. Of all sites, lower extremity flaps have the highest rate of failure [34]. Some of the prominent risk factors for flap microsurgery complications are co-morbidities such as diabetes, arteriopathy, and age > 60-years [31]. Eleven (65%) of the patients in this study had diabetes; ages varied from 19 - 79 years with five patients older than 60-years, and one patient had peripheral vascular disease [31]. Treatment with placental allografts in this study did not have the same complication profile seen in flap reconstruction and did not lead to the extraordinary lifestyle changes that transpire following amputations. The consequences of decisions that lower limb amputations are the most practical and inexpensive, do not always take into consideration individual future quality of life (QOL), or life changes, possibilities, and expectations [35]. There is "no one size fits all;" amputees may have a low hospitalization cost for the amputation, but a lifetime of prosthetic limb and wheelchair issues and expenses.

Prostheses are not always the best alternative for amputations; they must be appropriately constructed for the patient to adjust to limited functional capacity. With rehabilitation and therapy, physical attributes may become acceptable but frequently the mental aspects of recovery may severely impede the amputee's quality of life [36]. While an amputation may curtail hospital and medical costs at the time of injury, future medical costs for patients and society have been reported between $10,000 and $60,000 per prosthesis [37] [38]. The Veterans Hospital Administration (VHA) has vast experience with amputations from the past

Iraq and Afghanistan conflicts, which maimed our military personnel through improvised explosive devices (IED) [36] [37]. They have reported the medical costs to average $1.4 million per amputee [37] [38]. Among veterans with diabetes, the individual mean cost associated with a lower extremity amputation in the VHA system in FY2010 was $60,647 [38]. When inflated to 2020 levels via a consumer price index calculator (US Bureau of Labor Statistics), the adjusted mean cost would be $72,076 [39]. In diabetic foot ulcer treatment, the total extra healthcare costs of a lower extremity amputation versus no amputation, including a two-year follow-up, was between $40,000 and $60,000 [40]. For persons with a unilateral lower extremity amputation, the two-year health care cost, including initial hospitalization, inpatient rehabilitation, outpatient physical therapy, and the purchase and maintenance of a prosthetic device, was estimated to be $91,106 [41]. In a trauma study of 545 patients with a unilateral lower extremity injury, lifetime healthcare costs were higher for amputees ($509,275) than for those who had limb reconstruction ($163,282) [42].

Table 5, compares the advantages and disadvantages of these treatment modalities. Viewed from this perspective, the attempt to salvage the limb may be the

Table 5. Advantages and disadvantages of allograft placental membranes, flaps and prostheses.

dHACM/dHCM	Flaps/tissue transfers	Prostheses
	Advantages	
*Concurrent NPWT aids tissue regeneration and moisture management	No Immunologic products; autologous tissue used	Different types of prostheses available
Extremities retained	Immediate wound coverage with placement	Artificial limb or appendage
No other body parts used for healing or reconstruction	Potentially shorter LOS	Potentially shorter LOS
Improved Quality of Life		Treatment occurs out of hospital
Treatment easily transferred to outpatient setting		Wheelchair alternative
	Disadvantages	
Direct wound visualization is not possible while NPWT drape is in place.	NPWT cannot be applied over flap or tissue transfer; tissue regeneration and healing have no NPWT benefits.	Expensive acquisition costs
If NPWT applied improperly over healthy skin, it may lead to skin trauma or breakdown	Loss of a body part (muscle, skin) to cover wound; functional disability (walking; lifting oneself) due to lost muscle or skin	Increased lifelong expenses and healthcare maintenance
	Treatment cannot be transitioned to the outpatient setting until healing occurs	Impaired Quality of Life

*NPWT = negative pressure wound therapy. Advantages of NPWT are: 1) increases and expedites: granulation tissue generation; 2) increases vascularity; 3) removes pro-inflammatory biomarkers, produced by the body; 4). increases the flow of growth factors and nutrients to wounds.

most affordable option in respect to both the preservation of quality of life and lower economic impact compared to a major amputation. Depending on payer financial incentives, allograft cost can be justified because of superior outcomes and patient-recognized values in the fee for service environments, or directly on cost in environments where reimbursement is outcome-based or capitated across an episode of care for an injury. Overall, the economic impact of an extremity amputation is notably higher than the short-term costs of the allograft material, even when combined with the nominal product application costs [43].

5. Limitations

This study shares similar limitations to other studies in that it is retrospective, dependent on the accuracy of medical records, lacks patient heterogeneity, and is subject to selection bias. Despite these limitations, it has shown that placental allografts for limb salvage, such as dHACM and dHCM, have increased the resources available to progress one more rung on the surgical reconstructive ladder, before subjecting a patient with expose bones and tendons to amputation.

6. Conclusion

In select limb salvage cases, dHACM and dHCM were observed as a promising alternatives to amputations, tissue transfer flaps or other techniques for secondary intention resolution of extremity wounds with bone and tendon exposure. Additional studies are needed to determine whether the use of these products results in improved patient outcomes compared to current wound care techniques, tissue flaps or amputations.

Conflicts of Interest

William Tettelbach, MD is currently the acting Principal Medical Officer for the MiMedx Group, Inc. There are no other conflicts of interest to declare.

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