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Adjuvant hydrolyzed collagen powder in high-risk patients with large soft tissue defects undergoing orthoplastic limb preservation surgery

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ABSTRACT

Limb preservation in the multi-morbid patient remains a significant challenge. The combination of orthopedic and plastic reconstructive techniques ("Orthoplastics") is well known to result in limb preservation ("limb salvage") even in extremely high-risk patients. Despite advances, adjunctive healing techniques remain desirable.

In this case series, we examined the use of hydrolyzed collagen powder in limb salvage in multi-morbid patients undergoing limb preservation surgery. The medical records of ten high-risk patients with multiple co-morbidities undergoing limb preservation reconstruction, who would otherwise have required a major level amputation, were reviewed retrospectively. Of these patients, there was an average of nine varying risk factors, including the presence of infection, diabetes mellitus, renal impairment, vascular disease, smoking, illicit drug or alcohol abuse, or nicotine use. The case review data included patient demographics, risk factors, specific pathophysiology, Orthoplastic procedure, and the volume of adjunctive hydrolyzed collagen during the reconstructive procedures.

All patients achieved limb preservation or the prevention of an anticipated higher-level amputation. On average, two hydrolyzed collagen applications were used per patient with a mean volume of 1.8 g (range 2-4 g). Notably, the presence of an actively treated infection did not appear to diminish the efficacy of hydrolyzed collagen. Additionally, no adverse reactions were identified with the use of hydrolyzed collagen. These findings suggest that use of hydrolyzed collagen is a safe, valuable adjunct in Orthoplastic limb preservation surgery for patients at extreme risk for limb loss.

Introduction

Orthoplastic reconstruction of the lower extremity remains critical to limb preservation and quality of life in patients with both soft tissue and bone injuries. Unfortunately, most patients undergoing Orthoplastic limb preservation are at significant medical risk for impaired wound healing and complications at the reconstructive site due to trauma, infection, compromised healing mechanisms, malnutrition, diabetes, smoking, alcohol abuse, and other comorbidities. These risk factors, both modifiable and non-modifiable, increase susceptibility for a major level amputation if the Orthoplastic reconstruction is unsuccessful.[1–4] In patients with a pre-existing amputation, Orthoplastic reconstruction of the remaining limb is often required to prevent a higher level of amputation and maintain maximum residual limb function.[5,6] Impaired healing may lead to additional complications such as increased morbidities, unplanned additional surgeries, deterioration of existing medical co-morbidities, or eventual amputation.[7] Associated cost with amputations is estimated to be three times greater than those of limb salvage patients, providing substantial economic savings to the healthcare system, including surgical expense, prolonged rehabilitation, and ancillary care. The impact of amputation is often underestimated on a patient's quality of life, resulting in social isolation and depression.[8]

Due to the relatively urgent timing of limb preservation surgery, many modifiable risk factors can only be partially addressed and are

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often not able to be corrected appreciably prior to surgery. Additionally, in some patients, non-modifiable risk factors worsen with delays in surgery. Thus, adjunctive strategies during and post limb preservation surgery, to support soft tissue healing of the reconstructive site, are essential for improved outcomes. Supporting the healing processes is key to underlying health and survivorship of tissue repair. Utilization of products to support the soft tissue healing process, such as bovine type 1 hydrolyzed collagen powder, is critical to therapeutic interventions for limb preservation. Our case series review describes the use and benefits of hydrolyzed collagen powder in the healing of soft tissue reconstructions in a cohort of at-risk patients undergoing Orthoplastic limb preservation surgery.

Methods

Institutional Review Board approval was granted for this retrospective case series review. The records of 10 patients identified as being at high-risk for complications including possible amputation were reviewed. All patients presented with large musculoskeletal soft tissue injuries ($\geq$ 30 cm^2) associated with trauma, or infection, in combination with multiple co-morbidities, placing the patient at high-risk for limb loss. The study cohort received hydrolyzed collagen powder (CellerateRX® Surgical Powder, Sanara MedTech, Fort Worth, TX) as an adjunct to the surgical procedure and repair.

Patient demographics, medical comorbidities, and index limb pathology were analyzed. The overall reconstructive surgical effort used for limb preservation. As well as the specific reconstructive technique where a hydrolyzed collagen was utilized were recorded. Healing outcomes, limb preservation, and adverse events were recorded; numerical values were rounded to the nearest whole number.

Results

The study population's mean patient age was 57 years (range =

Table 1
Patient demographics, risks, pathology, wound size, orthoplastic procedures, hydrolyzed collagen use.

	Age gender	Disease state risks	Pathology	Wound size	Orthoplastic Reconstruction	**Adjuvant hydrolyzed collagen use; # of Applications; total volume (cc)**
1	38F	Foot/ankle crush & degloving & ST Infx 125 cm^2	Rev PB Flap; STSG; External Fixation	At I&Ds, Flap Recipient & Donor Site Beds; STSG Recipient Bed; 4 Applications: 0.5 + 1.0 + 1.5 + 1.0 g, **Total 4 g**		
2	29F	DM-1; AKI-3; HTN; Anticoag; Hx Poor Healing; MicroV Disease; Infx	Open/degloved ankle fracture & ST Infx+Osteo	65 cm^2	Rev PB Flap; STSG; External Fixation	Flap Donor Site, STSG Donor Site. 1 Application of 0.5 g/site, **Total 1 g**
3	68M	DM-1; AKI-2; CAD; HTN; Anticoag; Smoke; Hx Poor Healing; MicroV + MacroV Disease; Obesity; Infx	Charcot Neuroarthropathy; ST Infx + Osteo	30 cm^2	I&Ds; Bone Resection; Rev PB Flap; STSG; External Fixation	Flap Recipient Bed & Flap Donor Site. 1 Application of 0.5 g/site; **Total 1 g**
4	39F	AKI-3; Liver; Pulm; DIC; MSOF; Anticoag; Rhabdomyolysis; MicroV + MacroV Diseases (arterial & venous thrombosis); Obesity; Infx	Compartment Syndromes of Thigh, Leg & Foot; Pulseless Limb; Massive Myonecrosis; ST Infx	610 cm^2	Thrombectomies; Fasciotomies; Multiple I&Ds Skin, Fat, Fascia & Muscle; STSG's; Ankle Fusion; External Fixation	Leg & Foot Wounds prior to STSG. 4 Applications of 1 g, **Total 4 g**
5	73F	DM-2; CAD; HTN; Anticoag; Hx Poor Healing; MacroV & MicroV Disease; Emergency Bypass; Obesity; Infx	Massive Muscle & Skin Loss after Prolonged Ischemia: ST Infx	1092 cm^2	Multiple I&Ds Skin, Fat, Fascia & Muscle; Prolonged Instillation NPWD; STSG	Wound Surface Prior to STSG. 1 Application of 0.5 g/site; **Total 1 g**
6	70M	CAD; HTN; Pulm; Anticoag; Hx Poor Healing; MicroV Disease; Emergency Bypass; Infx	Ankle Fracture Incision Necrosis, ST Infx+Osteo	35 cm^2	Rev PB Flap; STSG	Flap Donor Site, STSG Bed. 1 Application of 0.5 g/site; **Total 1 g**
7	61M	AKI-2, Liver; CAD; HTN; Pulm; Anticoag; ETOH; PSAb; Infx Nutrition; Hx Poor Healing; MicroV Disease	Knee/Leg/Foot Fracture Fixation Wounds; ST Infx+Osteo	115 cm^2	Multiple I&Ds; Gastroc Flap & Fibula FF	Flap Donor Sites. 2 Applications of 0.5 g; **Total 2.0 g**
8	65M	DM-1; AKI-2; Liver; HTN; Pulm; Smoke; ETOH; Nutrition; Hx Poor Healing; MicroV Disease; Infx	Necrosis & Dehiscence Elbow Fixation Incision; ST Infx+Osteo	96 cm^2	I&Ds; FCU Flap; FTSG	Flap Donor Site, FTSG Donor Site. 2 Applications of 0.5 g/site; **Total 1 g**
9	66M	HTN; Pulm; Anticoag (coagulopathic); Nutrition; Infx (paraplegic)	Necrotic ST of Thigh/Knee/Proximal Leg; ST Infx+Osteo	875 cm^2	Multiple I&Ds; Resect Distal Femur; Foot Amputation; Fillet of Leg Flap	Surface of Muscle Flap (s). 1 Application of 2 g; **Total 2 g**
10	63F	DM-1; AKI-2; HTN; Anticoag; Hx Poor Healing; MicroV Disease; Infx	Necrotic Plantar Heel & Midfoot; ST Infx	150 cm^2	I&Ds; Rev Sural Flap; STSG	Flap & STSG Recipient Beds. 1 Application 0.5 g/site; **Total 1 g**

Legend: DM-1=type 1 diabetes; DM-2=type 2 diabetes**;** AKI= acute kidney injury-stage; CAD=coronary artery disease/cardiac dysfunction; HTN=hypertension; pulm=pulmonary dysfunction; liver=hepatic dysfunction; DIC=disseminated intravascular coagulopathy; MSOF=acute multi-system organ failure; Anticoag=anticoagulation therapy; smoke=active smoker; ETOH=alcohol abuse; PSAb=apolysubstance abuse; Nutri=nutritional deficit (abnormal labs/caloric intake/poor nutrients); Healing Hx=medical history poor healing; MicroV=micro-vascular disease; MacroV=macro-vascular disease; I&D= sharp excisional irrigation & debridements; ST Infx = soft tissue infection; Osteo = osteomyelitis
Rev PB flap=distally based reverse peroneus brevis muscle rotation flap; Gastroc flap=gastrocnemius muscle rotation flap; Fibula FF=fibula free flap; FCU flap=-proximally based flexor carpi ulnaris muscle rotation flap; revSural=distally based reverse sural fasciocutaneous rotation flap; LE Fillet flap=lower extremity fillet flap (multiple muscles on respective vascular axis); STSG=split thickness skin graft

29–73), with an equal gender distribution. All patients possessed multiple healing risk factors (mean = 9; range = 4–12) for complications that would otherwise result in a major level/high level of amputation. Seventy percent of patients had the presence of diabetes mellitus, with the majority of patients diagnosed type-1 (DMT-1) (50 %) and 20 % type-2 (DMT-2); 30 % smoked; 30 % abused alcohol; 20 % were substance abusers. Acute kidney injury (AKI) was also present with a mean AKI stage of 2 (range=2–3) with two patients requiring acute dialysis. Vascular disease (macro- and micro-vascular) was present in 90 % of patients; three patients required emergency vascular intervention: one direct vascular repair, one thrombectomy, and one patient requiring emergency bypass rendering regional soft tissue arterial perforators incompetent (Table 1).Four patients (40 %) had liver dysfunction, 90 % were hypertensive (HTN), 30 % had coronary artery disease (CAD), four patients (40 %) with pulmonary dysfunction, and one patient had acute multi-system organ failure (MSOF). All patients had a coagulation abnormality: one with disseminated intravascular consumptive coagulopathy (DIC), and nine (90 %) undergoing pharmacologic therapeutic or prophylactic anticoagulation with elevated blood coagulation values above normal reference ranges (Table 1). At surgery all patients were scored by the Society of Anesthesiologists Score Risk (ASA), with all patients having an ASA = 3.

All patients had an infection being actively treated. Furthermore, soft tissue infection (ST-Infx) was present in 90 % of patients, osteomyelitis was also present in 89 % of the cohort, a combination of both ST-Inx plus osteomyelitis was present in 78 % of patients. Culture-specific antibiotic therapy was initiated in all patients, averaging four weeks in duration. All patients had a soft tissue defect /reconstructive area with an average size of 319 cm^2 (range = 30–1092 cm^2).

Nutritional impairment (albumin/total protein below standard accepted values, poor caloric intake) was present in 40 % of patients with a history of a prior wound with poor wound healing was noted in 80 % of the population. Twenty percent of patients were obese (calorie rich-nutrient poor). These data are summarized in Table 1.

The index pathology resulting in the necessity for Orthoplastic reconstruction included trauma and trauma related incision/wound complications, complication of Charcot neuroarthropathy, prolonged compartment syndrome with rhabdomyolysis with AKI, vascular compromise and myonecrosis, acute arterial injury with resultant soft tissue necrosis, and wounds resulting from soft tissue infection or pressure injury wounds with infection (Table 1).

All patients underwent multiple soft tissue irrigations and debridement with negative pressure wound dressings as needed (range = 2–10). The resultant soft tissue defect to be reconstructed ranged from 10 to 1092 cm^2 (mean = 258 cm^2). An average of four operative settings (range = 2–10) were required to achieve limb salvage. Bone debridement was performed in all patients with osteomyelitis (89 %). Eight patients underwent a total of nine flap reconstructions: four patients underwent a reverse peroneus brevis muscle flaps with skin graft (to ankle); one patient had a gastrocnemius myocutaneous flap plus a free fibula flap (to the knee for a soft tissue defect and tibial plateau osteomyelitis); one patient underwent a reverse sural fasciocutaneous flap (to heel) and late delayed supplemental skin graft; one patient underwent a fillet of leg flap (four combined arterial pedicled muscle flaps) to the lower/mid-thigh; one patient had a flexor carpi ulnaris muscle flap and skin graft (to the elbow). The remaining two patients underwent lower extremity skin grafting over granulation tissue for soft tissue defects of 35 cm^2 and 1092 cm^2 (Table 1). Hydrolyzed collagen powder was used in all patients to support soft tissue healing at various phases of the Orthoplastic reconstruction. This included the acute application to both soft tissue donor sites and recipient beds for tactile adhesive properties supporting flaps and skin grafts, and application to deep and superficial tissue planes for the induction of secondary intention granulation before skin grafting. Hydrolyzed collagen was applied 1–4 times (mean = 2), with an average volume of 1.8 g. (range = 1–4 g) (Table 1). Notably, when drains were used, the mean drain output was 12cc over three days (excluding one exceptional hemopathologic patient outlier with thrombocytopenia and a concurrent requirement for full dose factor Xa inhibition, with a tissue healing bed on 875 cm^2). All patients went on to successful limb salvage (Fig. 1A–C) preventing a major-level amputation (Syme, below-knee amputation, above knee amputation), or prevention of hip disarticulation (Fig. 2A–F). In this cohort of patients, no adverse events were noted with the application of hydrolyzed collagen powder.

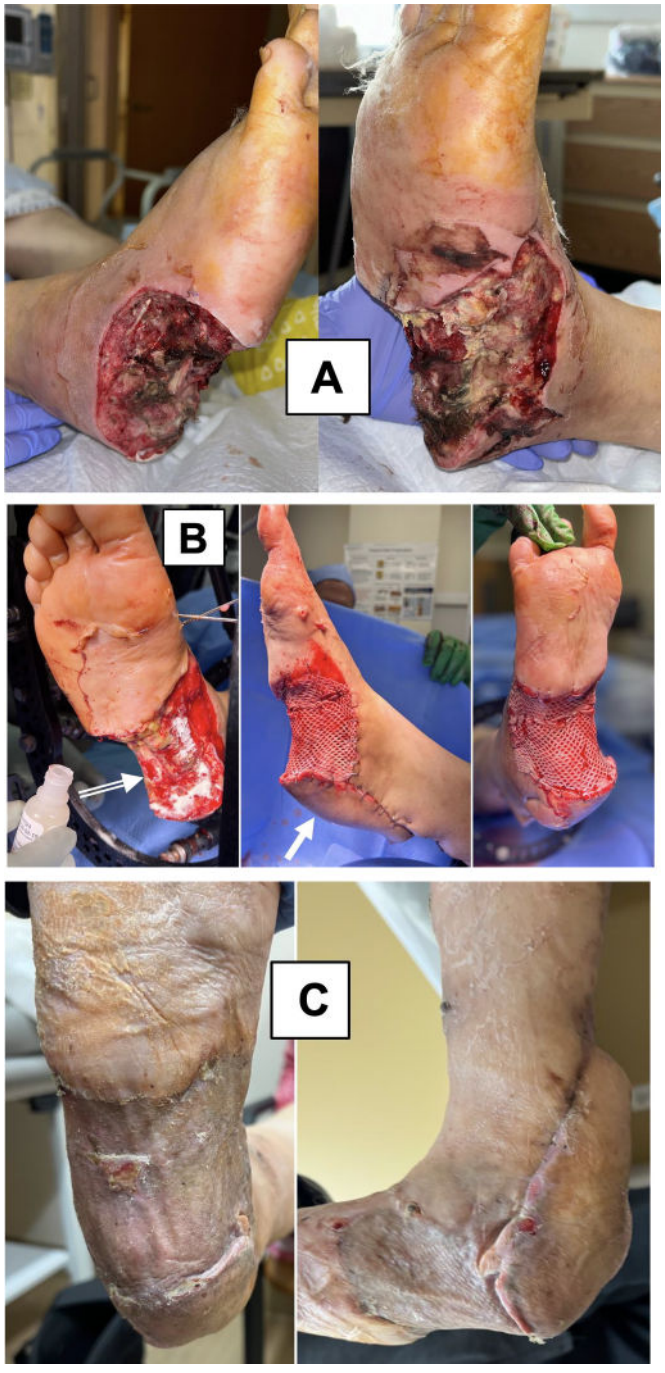

Fig. 1. A–C: Infected necrotic heel & plantar foot wound in a 62-year-old female with type-1 diabetes mellitus and multiple medical comorbidities **[A]**. After debridement, final Orthoplastic reconstruction was performed using hydrolyzed collagen (compound white arrow) applied to the wound bed just before inset of reverse sural fasciocutaneous flap (solid white arrow) & split thickness skin graft **[B]**; external fixation used for ambulation during healing. Final plantar & lateral photographs demonstrating successful limb preservation **[C]**.

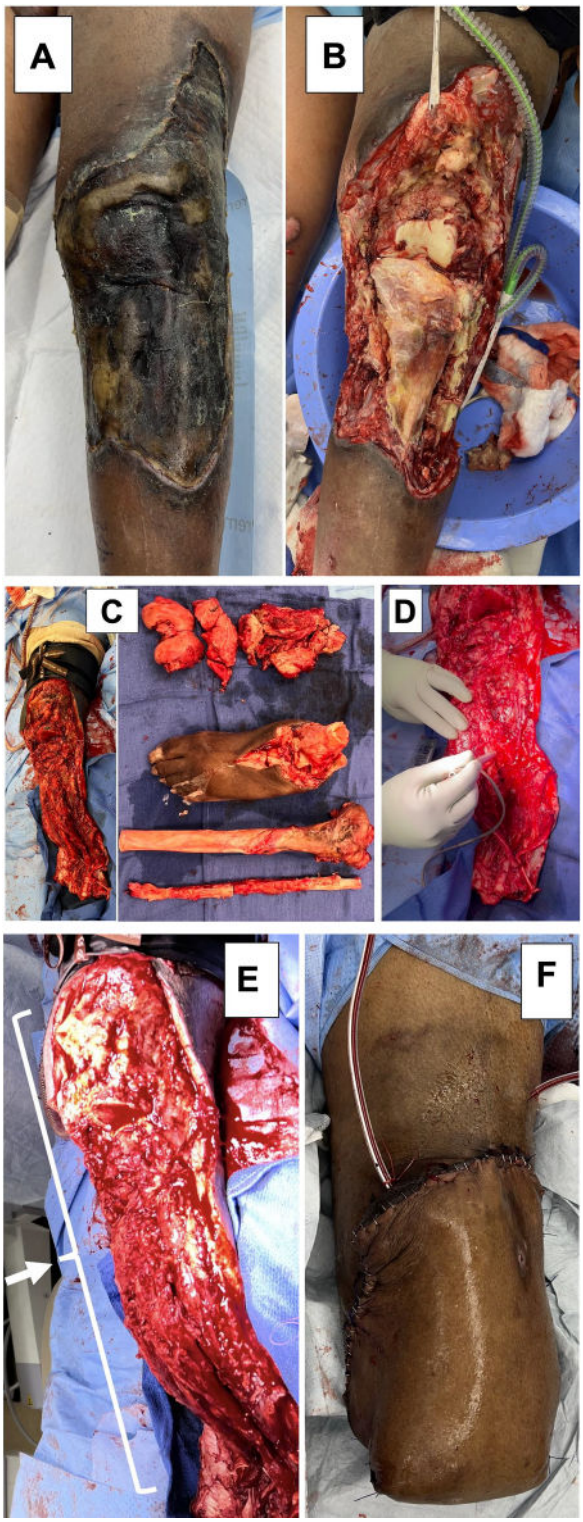

Fig. 2. A-F: Clinical pre-operative photograph **[A]** and initial debridement **[B]** of a septic 66-year-old male multi-morbid cervical spine injury patient with infected full-thickness soft tissue necrosis and femoral osteomyelitis. In the event of recovery of any lower extremity function, rather than a hip disarticulation, a lower-level amputation level was obtained by performing distal femoral resection, foot amputation & "fillet of leg flap" **[C]** comprised of multiple pedicled muscle flaps with accompanying skin perforators (note Doppler) **[D]**. Hydrolyzed collagen (visible white hued areas) was used to augment healing of entire tissue planes **[E]**, closed primarily **[F]**. Note the use of drains, as this patient was coagulopathic. The surgical site went on to heal uneventfully.

Discussion

Limb preservation in the multi-morbid patient is an extremely challenging venture. Multiple risk factors are associated with impaired healing,[7] and combinations of these risk factors are often present in patients presenting for limb preservation surgery. The Orthoplastic approach to limb preservation surgery utilizes both plastic surgery and orthopedic surgical techniques (often simultaneously) to reconstruct the musculoskeletal structures and the soft tissue envelope. In patients who have multiple risk factors for poor healing, as well as infection and anticoagulation, significant complications and failures may be commonplace and may lead to a major amputation. Thus, adjunctive therapies supporting soft tissue healing are a welcome addition to the surgeon's armamentarium.

Type-1 hydrolyzed collagen powder implemented for the application of collagen polypeptide fragments in surgical wounds has been shown to support a favorable wound healing environment due to its physical and chemical characteristics. Specifically supporting extracellular matrix production, bioactivity, immunomodulation, and recruitment of fibroblasts and keratinocytes to the site of injury. The molecular weight of hydrolyzed collagen is very low (3–6 KDa) and it has a pK (isoelectric point) value of 3.68–5.7, making it very soluble as compared to other collagen-based products.[9] The smaller size hydrolyzed collagen has many novel features such as solubility, angiogenic, antimicrobial, mitogenic, chemotactic, and adhesive properties.[9,12]

The capacity of hydrolyzed collagen to support, assist, or even accelerate soft tissue healing has been demonstrated in animal models.[10,11] Research has demonstrated improved perfusion of tissue, reduction of inflammation, and improved tensile strength of scar tissue.[12] Likewise, in human studies, hydrolyzed collagen preparations have been shown to support soft tissue healing in skin,[13] intra-articular tendons (i.e. rotator cuff, gluteus medius),[14] acute surgical wounds,[15] neurosurgical spine incisions[16–18] and joint arthroplasty incisions,[19] often negating additional complications as a result. In a large, case-matched cohort study of over 5300 elective procedures across multiple surgical specialties, such as would be seen in a typical hospital setting, the results demonstrated a near 60 % reduction in surgical site infection, most pronounced in clean elective cases.[20]

Collectively, hydrolyzed collagen demonstrates support to healing of elective surgical procedures in patients with a low to moderate number of risk factors. The data presented here exhibit the benefits of concomitant use of hydrolyzed collagen powder to support soft tissue healing in possessing a high number of risk factors (mean = 9) undergoing complex non-elective Orthoplastic limb preservation surgery. Additionally, all patients in the presented study had soft tissue and bone infections (with active on-going treatment) and large surface area wounds (mean size = 258 cm^2). While the observed data warrants a larger study into potential hemostatic attributes, hydrolyzed collagen is hypothesized to enhance function of the intrinsic or extrinsic coagulation cascades.

Surface area guidelines for the hydrolyzed collagen powder include a 1 g application for 271.13 cm^2 and the 5 g application at 1064.29 cm^2; however, this does not reflect wound depth and other individual characteristics of the surgical wound or procedure which impacts wound volume.[21] Although the exact volumetric proportion of hydrolyzed collagen powder has not been established, the presented data of this study reveal that for very large wounds (258 cm^2) a mean of 1.8 g of hydrolyzed collagen powder may be expected, with the provision that multiple applications may be required (mean =2). Thus, the senior author contends that the amount of hydrolyzed collagen powder must fully cover the entire surface area, spaced between tissue planes, and undermined wound edges. Conclusively, the volume of hydrolyzed collagen powder must be individualized to each case scenario and may require larger amounts of hydrolyzed collagen. In this cohort of patients, no adverse events were noted with the application of hydrolyzed collagen powder. The cost of care in limb preservation procedures can be high, with limb treatment costs correlating to the severity of limb threat;

however, amputation comes with a higher cost. Amputation can significantly impact quality of life and lower life expectancy, especially in the face of multiple comorbid conditions. The association between lower extremity amputations and premature mortality is well established, with an estimated five-year mortality following major lower extremity amputation ranging from 40 % to 90 %.[22] Comprehensive limb salvage programs have been shown to reduce the rate of amputations from 36 % to 86 %. Using the midpoint of this reduction (61 %) and accounting for the estimated cost of a limb salvage program ($1.7 billion) yields a cost savings of $26.8 billion.[23] The economic value of the addition of hydrolyzed collagen in limb salvage procedures should be further studied for its cost-benefit ratio as a component of care in these cases.

Conclusion

In summary, this report on a cohort of extremely compromised patients undergoing limb preservation surgery, adjunctive use of hydrolyzed collagen powder was found to have significant value in assisting with both the healing of soft tissue donor beds, recipient beds, as well as the generalized use for the creation of secondary granulation in preparation of skin grafts. There were no observed adverse effects, which further adds to the value of hydrolyzed collagen to aid in complex soft tissue reconstructions in limb preservation surgery. These data hold promise for further research into the benefits of hydrolyzed collagen to assist with soft tissue healing in the spectrum of surgical subspecialties. By supporting a conducive environment for healing, great potential exists for reduction in complications and improved patient outcomes, decreased length of hospital stay, and enhanced cost savings for healthcare systems.

Informed patient consent

Complete informed consent was obtained from the patient for the publication of this study and any accompanying images.

Declaration of competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The primary author of this paper received research funding of approximately $5000. No other competing financial interests for the remaining authors.

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