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Efficacy of collagen and elastin matrix in the treatment of complex lower extremity wounds

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Summary

Successful engraftment of skin grafts highly depends on the quality of the wound bed. Good quality of blood vessels near the surface is critical to support the viability of the graft. Ischemic, irradiated scar tissue, bone and tendons will not have the sufficient blood supply. In such situations flaps are to be resorted. However, the flaps also need to have good vascularity over the limbs. The introduction of dermal substitutes has provided a novel method for repairing various severe skin defects. These substitutes act as dermal regenerative templates, which facilitate dermal reconstruction and regeneration. This study was done to ascertain the effectiveness of these substitutes in the treatment of complex wounds. Between January 2022 and June 2023, 20 patients who had complex wounds, which could not be treated with simple skin grafting and who were treated with collagen and elastin matrix and split skin grafting (SSG) were retrospectively studied. The percentage of SSG take as per the records was noted at a 10-day post-operative period. Patient characteristics, comorbidities, duration and outcomes of the treatment were noted. Twenty patients were included in the study. The minimum size of the ulcer was 5 × 4 cm (area of 20 cm^2) and the maximum size of the ulcer was 15 × 15 cm (225 cm^2). Average take of skin graft was 93.7% at 10^{th} post-operative day. Recurrence at 6 months was nil. The scar quality was assessed by patient and observer at 3 months and 6 months post-operatively. The lower-limb ulcers with compromised surrounding tissue are complex. The major goal in these cases is to do simple surgery and prevent recurrence. The collagen and elastin matrices provide structural support for cellular infiltration, which helps maximize a SSG take and a stable long-term scar.

Key words

complex wounds – collagen – elastin matrix – arterial ulcer – venous ulcer

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Introduction

Partial thickness skin grafting is the most commonly performed surgical procedure for wound coverage. There are many advantages of this procedure, the most important being the simple technique. Successful engraftment of the skin graft depends on various factors. Availability of healthy wound bed and good vascular tissue in the vicinity are critical. In situations when these are compromised, the treatment of simple wound becomes challenging. These wounds are deemed to be complex to treat, which is described in literature but not defined uniformly. Most of the authors describe that these are the wounds, which have impaired circulation, either venous or arterial [1,2]. However, the pathology is multifactorial and not just a vascular compromise. In the majority of the times, plastic surgeons are referred to treat such wounds. Another major challenge that the surgeons face after split skin graft is providing long lasting results with good functional and cosmetic results [3]. Elastin fibers play pivotal role in the ultimate scar formation, they provide mechanical elasticity and reduce wound contraction and promote dermal regeneration [4]. The use of dermal substitutes is thought to increase the collagen elastin content in the wound bed. Hence, they aid in improving the functional as well as cosmetic outcomes in split skin grafted wounds. In this work we intend to study the effect of collagen and elastin matrix and split skin grafting (SSG) in the treatment of deemed to be complex wounds.

Materials and method

Between January 2022 and December 2023, 20 patients who had complex wounds (with either venous/arterial or combined deficits) were treated with collagen – elastin matrix along with SSG. All the patients underwent arterial and

Tab. 1. Demographic profile of the patients.

Serial number	Sex	Age	Site	Arterial	Venous	Size (cm)	Area (cm²)	Graft take	Duration (days)
1	M	55	LL	Y	–	3 × 8	24	95	16
2	M	65	LL	Y	–	4 × 7	28	90	19
3	M	43	LL	Y	–	5 × 4	20	96	12
4	M	63	LL	Y	–	8 × 6	48	100	10
5	F	63	LL	Y	–	4 × 7	28	95	17
6	M	44	LL	Y	–	3 × 8	24	92	18
7	M	61	LL	–	Y	15 × 15	225	90	19
8	F	59	LL	–	Y	6 × 14	48	90	22
9	F	53	LL	–	Y	12 × 10	120	97	17
10	M	58	LL	–	Y	8 × 6	48	93	21
11	M	42	LL	–	Y	4 × 10	40	100	10
12	M	61	LL	–	Y	9 × 12	108	95	19
13	M	48	LL	–	Y	12 × 12	144	92	22
14	M	65	LL	Y	Y	3 × 12	36	92	22
15	M	68	LL	Y	Y	5 × 6	30	98	12
16	F	70	LL	Y	Y	13 × 15	195	90	19
17	F	61	LL	Y	Y	7 × 5	35	98	14
18	M	59	LL	Y	Y	8 × 9	72	96	14
19	M	54	LL	Y	Y	4 × 5	20	85	26
20	F	56	LL	Y	Y	6 × 6	36	90	15

Average duration for healing 17.2 days. M – male, F – female, LL – lower limb, Y – yes

venous doppler studies to ascertain arterial or venous insufficiency. None of the patients underwent treatment for arterial or venous pathology. The percentage of SSG take at 10th post-operative day was noted. Patient characteristics, comorbidities, duration of the treatment and outcomes were noted. The scar following was assessed using POSAS questionnaires.

Inclusion criteria

Patients with ulcers, which warrant skin grafting along with one of the following comorbidities were included in the study:

1. patients with radiologically proven varicosities;
2. patients with peripheral arterial disease;
3. patients with both combined;
4. patients with exposed tendon or bone up to 4 cm².

Exclusion criteria

Patients who refused the use of matrix as a treatment.

Detailed surgical procedure

On day 1 ulcers were thoroughly debrided and after complete hemostasis, collagen and elastin matrix was applied. The pressure dressing was applied. NPWT was used in patients with varicosities for 5–7 days. Patients with arterial compromise are treated with pressure dressing only. Once the wound was healthy then skin grafting is performed. Post-operatively, the dressing was changed at 5th, 8th and 10th day. The percentage of skin graft take was noted at 10th post-operative day. The patients were followed up for 6 months. The scar outcome for quality is assessed using the POSAS questionnaire 6 months post-operatively.

Results

Twenty patients were included in the study – 13 males and 7 females, their age ranged from 42 to 70 years. Multiple ulcers were treated in 6 patients, 14 patients with a single ulcer. Seven patients had varicose ulcer, 6 patients had ischemic ulcers (arterial), 7 patients had

Tab. 2. POSAS score mean and standard deviation for all patients.

Observer score			Patient score		
parameters	**mean**	**STD dev**	**parameter**	**mean**	**STD dev**
vascularity	1.05	0.22	pain	1.65	0.79
pigmentation	1.95	0.67	itching	1.7	0.71
thickness	1.1	0.3	color	1.75	0.70
relief	1.05	0.22	stiffness	1.1	0.3
pliability	1.25	0.43	thickness	1.2	0.4
surface area	2.1	0.3	irregularity	2.4	0.49
overall	1.7	0.64	overall	1.85	0.65

combined arterial and venous deficiencies. Four patients had exposed tendon or bone in the floor. The minimum size of the ulcer was 5 × 4 cm (20 cm^2) and the maximum size was 15 × 15 cm (225 cm^2). The average take of the skin graft was 93.7% at 10th post-operative day (Tab. 1). The average duration of healing was 17.2 days. None of the patients had recurrence of ulcer at a 6-month follow-up. The scar quality assessed by patient and observer at 3 months and 6 months post-operatively (according to the POSAS questionnaire; Tab. 2). The mean overall grading of the scar by the patients and the observer at 6 months was 1.85 and 1.7, respectively.

Discussion

As described by Neligan, successful engraftment of skin grafts highly depends on the quality of wound bed [5]. "A good quality of blood vessels: near the surface is critical to support graft viability". But these ideal conditions will not be there in some of the patients. Such patients pose a challenge for skin grafting. Similarly, patients with wounds, which have tendons or bone exposed are not candidates for skin grafting. They would need a flap for wound cover. However, in conditions where the local or regional tissue is damaged due to irradiation, or in avulsion injuries, this may not be possible. A simple wound with 1–2 cm of bone or tendon exposed becomes complex to treat and needs more distant or free flaps. An extra-cellular matrix plays a pivotal role in normal wound healing. A dermal extra cellular matrix has various structures and chemicals, which are arranged in a specific manner [6]. These act as a guiding scaffold for the reparative cells to in-grow and lay in an organized manner [7]. In complex situations like ischemia, irradiation, or chronic ulcers, the extra cellular matrix is often dysfunctional and hence the cellular ingrowth suffers [8]. This extracellular matrix dysfunction is caused not only by non-availability of a scaffold for tissue regeneration but also by a lack of signaling proteins [9]. These proteins are crucial for intercellular communication so that the vascular and cellular ingrowth occurs in organized manner. Hence the ideal matrix should not only provide structural support but also should comprehend the intra cellular, biochemical communication so that it can guide the active skin regeneration [10].

More than 75 types of skin substitutes are available commercially [11]. They are classified as class I/II/III by Kumar et al. [12]. Class I and class II epidermal substitutes are disadvantageous as they are fragile and lack mechanical stability [13,14]. Dermal replacement substitutes provide a more durable scaffold [12]. All these substitutes claim to form neo-dermis at various intervals. Although all of them perform the same function, there are various histopathological differences during the healing process. These matrices have a varied composition collagen only matrix, collagen-elastin matrix, cross-linked collagen matrix and human acellular dermal wound matrix, to mention some of them.

Bio-engineered dermal substitutes vary in chemical composition as well as structure. In our study we used single layer collagen – an elastin hydrolysate matrix. The collagen in these matrices was in a non-cross-linked state. This has several advantages as compared to cross-linked matrices or a cellular dermal matrix. Chemical cross-linking of the collagen fibers is resistant to easy degradation, whereas the non-cross-linked scaffolds tend to lose the thickness soon and allow vascular ingrowth. The angiogenesis occurs with increased vascular lumen and reduced vessel density. As described in literature, non-cross-linked substitutes are better compared to crosslinked ones for cellular infiltration and vascular ingrowth, which in turn helps the SSG uptake [15]. Other bio-engineered dermal substitutes are all cross-linked collagens with chitosan, glycosaminoglycans. This cross-linking delays the breakdown of the matrices and hence plays a major role when the durability of the matrix is concerned [16]. As compared to bio-engineered scaffolds, human acellular dermal matrices (HADM) are biological

Fig. 1. A 40-year-old male with varicose ulcer treated with matrix and SSG had a 100% take at 10th post-operative day and a good scar outcome at 6 months post-operatively.

Fig. 2. A 61year-old female with DVT, varicosities and APLA vasculitis treated with matrix and SSG had scar which had near-to-normal skin features.

materials which also provide the scaffold for vascular ingrowth. However, the vascular ingrowth was less compared to the bio-engineered matrix in animal studies [17,18]. The presence of a basement membrane was found to hinder the cellular infiltration and also the HADM with a basement membrane was prone to immune response [19]. Since the vascular ingrowth is lower, the SSG uptake is also affected. After this extensive literature search, we decided to use these substitutes, which are non-cross-linked collagen along with elastin matrix. Since the presence of elastin helps in the final scar outcome, this combination was ideal to use for the treatment of complex ulcers.

As per the study by Urciuolo et al. [20], the combination of non-cross-linked dermal substitute and SSG had the skin graft take rate at 100%. Similarly, a study by Min et al. had a graft uptake of 96.7% [21]. Nevertheless, in another study by Thyung Min Haln et al. [22], the take was 90% with acellular dermal matrix. In our study, the ulcer size varied from 20 to 225 cm^2 and the graft take rate was 93% (Fig. 1–3). Among these studies the acellular dermal matrix study showed a lower SSG uptake. Although in our study the take was 93% in average, the ulcers completely healed after regular dressing. None of the patient needed regrafting surgery to heal the wound and none of our patients had recurrence of the ulcer either, which is a known characteristics in venous or arterial ulcers. Almost all the patients scored the SSG as near to normal skin after 6 months. These dermal substitutes play a crucial role in the stability of SSG and even ultimate SSG maturation scar formation. The presence of elastin would increase the elasticity as well as the resilience of the skin [23]. The resultant scar quality after SSG was hence better when used along with these dermal substitutes, especially the one with collagen-elastin combination [24]. In a histological study, usage of elastin scaffold showed that the elastin content was present more in patients treated with SSG alone or scars of secondary intention [25]. But it was a half of the normal skin or FTSG, which indicates that even after these matrices or SSG the normal elasticity of the skin could not be achieved. Lempert et al.

Fig. 3. A 63-year-old female with monophasic arterial flow suffered a distal third leg open type 3B fracture, both bones underwent cross-leg flap, which necrosed leaving a 7 × 4 cm ulcer with exposed tibia. The patient was treated with a matrix and SSG.

used these collagen-elastin matrices as one stage or two stage procedure along with SSG. They concluded that the resultant skin was highly stable and had elasticity for the soft tissue coverage [26]. Many other studies by Min et al. [22] and Ryssel et al. [27] opined that the resultant scar after the use of collagen-elastin matrix had less propensity to hypertrophy or keloid formation. Watfa et al. concluded in their study that these matrices are known to increase the elasticity of SSG, making it a nearly normal skin [28].

The POSAS scale is used for the scar assessment. We adapted the same for the SSG and resultant scar. Patients scored parameters such as pain, itching, color, stiffness and thickness as near to normal and scored irregularity at a higher score but all were satisfied with the result and scored overall end result as near to normal. Twenty patients mean overall score was 1.85. The observer mean overall score was 1.7. The observer also scored pigmentation and the surface area as deviated from the normal skin. But both observer and the patients scored as near to normal skin at 6 months post-operatively. In the present study it is observed that SSG used along with collagen/elastin matrix in complex wounds increase the uptake percentage of the SSG. Also, the final scar at post-operative 6 months had good elasticity. Hence, the use of the matrix and SSG is beneficial but larger number studies would be required to authenticate the results.

Conclusion

The treatment of ulcers associated with impaired circulation is a challenge. Similarly, the ulcers with compromised surrounding tissue are complex as well. The major goal in these cases is to do a simple surgery and prevent recurrence. The collagen and elastin matrices provide structural support for vascular ingrowth in initial phases. The uniform angiogenesis occurring after the application of matrices helps to maximize the SSG take. Additionally, the SSG scar quality following these matrices application is highly satisfying for the patients. However, comparison of the patients with those treated without using these matrices would give a better insight into the cosmetic outcomes.

Roles of the authors

Manjunath Kalapurmatt Nagabhushanaiah – design of the article and corresponding author;
Nisarga Venkatachala – data collection and analysis;
Mysore Srinivas Venkatesh, Sanmathi Parasuramulu, Shanthkumar Shivalingappa – performing surgeries, clinical investigators.

Limitation of the study: The study population number is low, a large number of prospective studies is required to authenticate the results. Further, the follow-up of patients beyond 6 months is required to ascertain the long-term efficacy of matrix.

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