Soft Tissue Reconstructions with Dermal Substitutes Versus Alternative Approaches in Patients with Traumatic Complex Wounds

Umberto Morozzo · Jorge Hugo Villafañe ·
Giandavide Ieropoli · Silvia Chiara Zompi ·
Joshua A. Cleland · Massimo Navissano · Fabrizio Malan

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Abstract The use of dermal substitutes is considered an effective treatment in several pathologies involving skin damage, mainly extensive burns and trauma. Treatment alternatives entail performing flaps or autografts. The purpose of this cross-sectional study is to assess the clinical effects and cost-effectiveness of dermal substitutes in surgical procedure in complex wound healings of adult trauma patients. The study includes 52 patients who received dermal substitutes ($n=25$) between 2007 and 2012 and patients treated between 2006 and 2011 who received standard treatment ($n=27$). All patients presented with posttraumatic soft tissue defects with bone and/or tendon exposure. Differences in costs, mean

differences in Euros and Euros per square centimeter, and clinical data were collected as outcome measures. Pearson's correlations were used to assess the relationship between total costs with sociodemographic data and clinical services to different healthcare providers (clinical data and costs were recorded for both groups). No relevant differences on acceptance rates were noticed amongst groups. Surgery costs were shown to be significantly reduced in the dermal substitutes group ($P<0.01$) even though total costs (surgery+hospitalization) did not exhibit a significant difference. Surgical time was significantly reduced in the dermal substitutes group (1.81 min/cm² lesions) as compared with the standard group (6.08 min/cm² lesions). The current study suggests that not only clinical but also possible economic and logistical advantages in choosing dermal substitutes may exist.

U. Morozzo
Ospedale San Lazzaro, Turin, Italy
e-mail: umberto.morozzo@gmail.com

J. H. Villafañe (✉)
IRCCS Don Gnocchi Foundation, Milan, Italy
e-mail: mail@villafane.it

G. Ieropoli · S. C. Zompi · M. Navissano · F. Malan
General Plastic Surgery, CTO, Turin, Italy

G. Ieropoli
e-mail: ieropoli.giandavide@gmail.com

S. C. Zompi
e-mail: silviachiara.z@gmail.com

M. Navissano
e-mail: navissano@alice.it

F. Malan
e-mail: f.malan@fabriziomalan.it

J. A. Cleland
Department of Physical Therapy, Franklin Pierce University,
Concord, NH, USA
e-mail: joshcleland@comcast.net

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Introduction

The term dermal substitutes refer to a specific type of skin substitutes that may replace the physiological dermal component present in human skin. The majority of dermal substitutes are acellular matrices, whether allogenic, xenogenic, or synthetic [1] and can be single or double layered. These bioengineered devices act as structural and biochemical template for wound healing [2] by inducing dermal reconstruction through an increased level of local growth factors, encouraging cellular proliferation and differentiation (in particular

keratinocytes) thus promoting the formation of an intact and functional basement membrane [3, 4].

The use of dermal substitutes is today considered an effective and useful treatment in several pathologies involving skin damage, mainly extensive burns [5–7] and trauma [8, 9] and also venous and chronic ulcers [10–12], scar reconstructive surgery [13, 14], abdominal wall repair [15–17], esthetic reconstructions, dermal excision surgery [18, 19], and breast implants. Despite such great possibilities of dermal substitutes, universally accepted clinical guidelines have not been developed yet for complex wounds in patients who have experienced severe trauma. The majority of literature related to traumatic injuries usually focuses on analyzing the devices and results obtained on different clinical contexts rather than focusing on this specific illness, so it is not possible to recommend a clinical standardized approach to patients who have experienced severe trauma.

Perhaps another reason as to why this type of reconstructive approach may not be utilized more than others relates to the initial *cost of purchase* for the device. The approximate cost of 5×5 cm double-layered matrix is about €800, and this clearly does not encourage the choice of dermal substitutes as first-line therapy.

The primary objective of this study was to compare the clinical effectiveness of a surgical approach with dermal substitutes reconstruction relative to surgery procedures considered “gold standard” in the treatment of complex wounds with bone and/or tendons exposure (poor vascularization surfaces) in adult patients. The secondary aim was to examine the economical impact of using dermal substitutes versus alternative procedures.

Methods

From November 2007 to June 2012, all patients ($n=25$) referred to the Department of Plastic Reconstructive Surgery in three different highly specialized University Hospitals in Italy (Azienda Ospedaliera Universitaria “S. Giovanni Battista” (TO); Azienda Ospedaliera Universitaria “Maggiore” (NO); Azienda Ospedaliera “Maria Adelaide-C.T.O.” (TO)), were invited to participate in this prospective study. All patients were treated with dermal substitutes technique, following a standard surgical protocol described below. Informed consent was obtained from all participants, and procedures were conducted according to the Declaration of Helsinki.

Additionally, between July 2006 and August 2011, we collected data on all adult patients (18–76 years old) with same clinical characteristics that underwent different surgical procedures (local flaps, free flaps, or dermo-epidermal autografts), today considered as “gold standard” procedures ($n=27$) that were treated as hospitalized at the Department of Plastic Reconstructive Surgery in three different highly specialized

University Hospitals in Italy. Surgical procedure was determined by general consensus of at least two plastic surgeons with at least 20 years of experience and between location and signs of infection in addition to patient’s general condition.

Patient demographics and characteristics were recorded for every subject and are summarized in Tables 1 and 2. We considered the time limits of surgical procedures as the time of the first incision to the placement of the final suture. Days of hospitalization have also been calculated starting from the day of first intervention. Engraftment rates and clinical or surgical complications were also carefully recorded for each subject.

The costs within the healthcare sector were calculated using the fees paid to referring hospital for patients registered in the region of Turin and included overhead costs using year 2012 prices. The fees were €10.19 per elective operative

Table 1 Baseline demographics for both groups

	Dermal substitutes ($n=25$)	Standard ($n=27$)	Total ($n=52$)
Age (means years, SD)	50±18	44±18	46±19
Gender (M/F)	14/11	4/23	18/34
Smoke (n) (46.2 %)	13 (52.0 %)	11 (40.7 %)	24
Comorbidities (n) (30.8 %)	9 (36.0 %)	7 (25.9 %)	16
Trauma location (n)			
Head	0 (0.0 %)	1 (3.7 %)	1 (1.9 %)
Arms	3 (12.0 %)	4 (14.8 %)	7 (13.5 %)
Legs (84.6 %)	22 (88.0 %)	22 (81.5 %)	44
Exposure (n)			
Bone (34.6 %)	8 (32.0 %)	10 (37.0 %)	18
Tendons (25.0 %)	7 (28.0 %)	6 (22.2 %)	13
Bone and tendons (40.4 %)	10 (40.0 %)	11 (40.7 %)	21
Etiology (n)			
Motorcycle accident (30.8 %)	7 (28.0 %)	9 (33.3 %)	16
Car accident (23.1 %)	6 (24.0 %)	6 (22.2 %)	12
Home injury (28.8 %)	9 (36.0 %)	6 (36.0 %)	15
Work injury	2 (8.0 %)	5 (18.5 %)	7 (13.5 %)
Sport injury	0 (0.0 %)	1 (3.7 %)	1 (1.9 %)
Aggression	1 (4.0 %)	0 (0.0 %)	1 (1.9 %)

Data are expressed as means±standard deviation (SD)

n number of patients

Table 2 Clinical data

	Dermal substitutes (n=25)	Standard (n=27)	Total (n=52)
Lesions number	1.24	1.00	1.12
Lesion dimensions (cm ²)	35.8	27.1	31.3
Anesthesia			
General (29.7 %)	4 (8.9 %)	11	
Sub-arachnoid block (40.5 %)	23 (51.1 %)	15	
Nerve block	7 (15.6 %)	6 (16.2 %)	–
Local	9 (20.0 %)	5 (13.5 %)	–
Dermal substitute			
Double layer	20 (80.0 %)	–	–
Single layer	5 (20.0 %)	–	–
Surgery time			
Min	46.3	142.8	–
Min/cm ²	1.81	6.08	–
Take rates			
Dermal substitutes	94	–	–
STSG-Thin	93	–	–
Combined	93	–	–
Standard surgery	–	91	–
Standard surgery (1st surgical revision)	–	99	–
Standard surgery (2nd surgical revision)	–	100	–
Combined	–	93	–
Complete healing			
Days	70.1	67.69	–
Days/cm ²	2.51	2.74	–
Surgical revision needed	2 (8.0 %)	7 (25.9 %)	–

(surgery) minute and €493.28 per the cost of the length of stay in the hospital per day.

Details of healthcare costs were retrieved from the patient's records. In addition, we collected information about the nationality, age at the time of injury, sex, date and place of injury, etiology, and diagnosis.

We constructed three case categories that correspond closely to costs strategies. These were (A) surgery, (B) length of stay, and (C) total healthcare cost. The study includes all 52 patients from 2007 to 2012 dermal substitutes and 2006–2011 standard groups.

To be included in the study, patients had to suffer posttraumatic soft tissue defects with bone structures and/or tendon exposure with absence of necrotic tissue of the wound bed after debridement (either medical or surgical), and the diagnosis had been confirmed by at least two surgeons. Patients under the age of 15 were not included in this study. Patients who did not have an optimal wound bed (as described in surgical protocol) were considered excluded. Other exclusion

criteria included poor compliance to the clinical protocol or patients with degenerative or non-degenerative neurological conditions in which pain perception was altered.

Devices

Two different bioengineered devices were chosen to be applied on wound surfaces:

- Integra Double-Layer 2.3 mm thickness, with silicone protective sheet, to be used in a two-stage procedures;
- Matriderm Single Layer 2 mm thickness, to be used in a one-stage procedure.

Surgical Protocol The surgical protocol followed consisted of:

- First evaluation of the patient and wound for inclusion in the study, according to the criteria expressed above;
- Identification of the optimal dermal substitutes after careful analysis of the type of patient and the type of wound. Standard choice was represented by Integra Dermal Regeneration Template DL (due to the fact that its thickness, higher than MATRIDERM SL, is more suitable in complex cases of injury, especially in load points or joints); the application of MATRIDERM SL was performed only in cases where the wound bed appeared to be uncontaminated at first presentation, with small dimensions (not exceeding 35 cm²) and the patient was not affected by any chronic disease involving blood vessels.

In case of DL dermal substitute application, we performed:

- Antibiotic presurgical treatment with 2 g intravenous (i.v.) Ceftriaxone, continued after procedure depending on patient's general condition and local wound.
- Accurate surgical debridement of crushed or non-viable tissue until reaching a viable and aseptic bed, basing on TIME scheme [20, 21].
- Dermal substitute application, performed after wound's bed cleaning for several minutes (not more than 5) with saline solution and preparation of the device while preserving 1 mm of margin on each side.
- Fixing with metal staples and *dressing with petroleum gauze* directly in contact with the matrix. The final coverage is obtained by normal patch or non-compressive bandage in case of larger lesions.
- Postsurgical check within 24 h from the application without modification of the dressing and hospital discharge after clinical evaluation of the patient's general condition

- (f) At discharge, antibiotic therapy was with amoxicillin+clavulanic acid 1 g two times/day for 6 days.
- (g) Monitoring outpatient weekly or bi-weekly (up to 4 weeks from the time of the application of the matrix).
- (h) Second hospitalization 4 weeks after the application and check of the neodermis in order to plan a definitive surgical coverage with thin split-thickness skin graft (STSG-Thin, 0.008–0.012 in. or 0.2–0.3 mm).
- (i) Antibiotic presurgical treatment with 2 g i.v. Ceftriaxone, continued after procedure.
- (j) Surgical removal of the protective silicone film, neodermis cleaning with saline solution, and application of STSG-Thin (either obtained by Blair knife, classic dermatome, or Padgett's electric dermatome).
- (k) Fixing STSG-Thin with metal staples and moulage technique.
- (l) Postsurgical check at 24–48 h from application and hospital discharge after clinical evaluation of the patient's general condition, as practiced in the first surgical step, with preservation of dressing for at least 7–8 days.
- (m) At discharge, antibiotic therapy was set up with amoxicillin+clavulanic acid 1 g two times/day for 6 days
- (n) Monitoring outpatient after a week and then once a week at least (number of meetings varies according to the mobility and availability of the patient, as well as the specific conditions of the reconstructed area) and dressing change every 2–3 days for the first 2 weeks and later in a personalized way until full recovery.
- (o) Follow up at 1, 3, 6, 12, and 24 months from the STSG-Thin application.

The SL dermal substitute procedure was performed following the same steps, reaching instead a complete coverage applying both the bioengineered matrix and STSG-Thin in the same surgical procedure. The same follow-up methods and monitoring were performed as described above.

Data Analysis

Statistical analysis was performed using SPSS (version 20.0 for Windows, SPSS, Inc. Chicago, IL, USA). Independent samples *t* tests and paired samples *t* tests were performed to assess differences in outcomes between groups. Regression analyses were also used to determine independent predictors of outcomes. Significance was set at $P < 0.05$. The Kolmogorov–Smirnov test confirmed the normality of the distribution of the data, so a repeated measures analysis of variance (ANOVA) was used to determine the differences in costs as the within-group factor (dermal substitutes group or standard group). The main hypothesis of interest was the between-group interaction. Between-group differences were expressed as mean differences in Euros and Euros per square centimeter with 95 % CIs. Pearson's correlations were used to assess the

relationship between total costs with sociodemographic data and clinical services to different healthcare providers were performed.

Results

A total of 52 patients (mean±SD age, 46±19 years; 53 % female) with an age up to 83 years were included in the study; 11 men and 14 women aged 18 to 76 years (mean, 50 years; SD, 18), formed the dermal substitutes group; 23 men and 4 women aged 15 to 83 years (mean, 44; SD, 18) formed the standard group. No significant differences for sex, lesion number and dimensions, or age ($P > 0.05$) were noted. The demographic and clinical data of each group are detailed in Tables 1 and 2. A normal distribution was confirmed with Kolmogorov–Smirnov test ($P > 0.05$). No subjects dropped out during the different phases of the study, and no adverse effects were detected after the treatment.

Clinical

Regarding clinical results, a statistically significant difference was not identified between the two groups, considering as successful the event of an engraftment rate of ≥ 90 % as illustrated in Table 2. Complications instead showed some differences between groups, mainly regarding scarring and infections rates, as shown in Table 3.

Table 3 Complications

	Dermal substitute (<i>n</i> =25) <i>n</i> (%)	Standard (<i>n</i> =27) <i>n</i> (%)	Total (<i>n</i> =52) <i>n</i> (%)
Pathological scarring	6 (24.0 %)	2 (7.4)	8 (15.4)
Pain at dressing change	3 (12.0)	4 (14.8)	7 (13.5)
Partial engraftment (< 75 %)	3 (12.0)	4 (14.8)	7 (13.5)
Wound dehiscence (partial or total)	2 (8.0)	2 (7.4)	4 (7.7)
Bleeding	2 (8.0)	3 (11.1)	5 (9.6)
Partial engraftment (< 50 %)	2 (8.0)	2 (7.4)	4 (7.7)
Superficial infection	1 (4.0)	4 (14.8)	5 (9.6)
Perilesional skin suffering	1 (4.0)	1 (3.7)	2 (3.8)
Allergic reaction	1 (4.0)	0 (0.0)	1 (1.9)
Deep infection	0 (0.0)	0 (0.0)	0 (0.0)
Foreign body reaction	0 (0.0)	0 (0.0)	0 (0.0)
Engraftment failure	0 (0.0)	0 (0.0)	0 (0.0)
SIRS	0 (0.0)	0 (0.0)	0 (0.0)

Healthcare and Costs

Patients receiving care through the dermal substitutes experienced 0.81 times the number of lesions (1.01 versus 1.24) and 0.32 surgery minutes (46.3 versus 142.8) compared with the standard group. Dermal substitute patients also had 0.97 times the number of days in the hospital (9.71 versus 9.96). With respect to complete healing, days in the dermal subgroup were 0.97 (67.7 versus 70.1) times the number of days as the standard group. The differences between the two groups of patients were statistically significant ($P<0.05$) for the surgery time.

A summary of cost differences between groups is presented in Table 4.

• Surgery

Univariate results demonstrated that the cost of surgery for the dermal substitutes group was significantly predicted by the interaction between group ($F_{(1,00)}=27.55$; $P<0.001$; partial $\eta^2=0.38$). The mean plot for the interaction term is displayed in Fig. 1. Patients treated with dermal substitutes showed lower cost in Euros and Euros per square centimeter as compared with the standard group (all, $P<0.01$).

• Length of stay

Regarding the results of the cost of length of stay of the dermal substitutes group, the ANOVA revealed that there was not a significant group factor ($F_{(1,00)}=0.51$; $P=0.5$; partial $\eta^2=0.011$). The post-hoc testing revealed no significant

Fig. 1 Total healthcare cost

difference in cost in Euros and Euros per square centimeter as compared with the standard group (all, $P>0.05$).

• Total healthcare cost

The cost outcomes for healthcare did not exhibit a significant group factor ($F_{(1,00)}=0.57$; $P=0.46$; partial $\eta^2=0.012$). The post-hoc testing revealed that cost in Euros and Euros per square centimeter was not statistically significant between groups (all, $P>0.05$). See Fig. 1.

Bivariate correlations between total costs with sociodemographic characteristics and clinical services to different healthcare providers were analyzed. There was a significant correlation between total cost and lesions (cm^2 ; $r=0.52$; $P<0.001$), surgery time (min; $r=0.57$; $P<0.001$),

Table 4 The healthcare cost per patient (EUR) of treating several trauma injuries in 52 adult subject

	Dermal substitutes Mean SD	Standard Mean SD	P value ^b	95 % confidence interval	Cost ratio ^c
Surgery					
€	467.21±154.1	1454.91±795.6	<0.001 ^a	778.96–1143.16	0.32
€/cm ²	21.04±9.3	61.90±21.0	<0.001 ^a	35.23–47.71	0.34
Dermal substitutes (means)					
€	839.4±488.4	–	–	–	–
€/cm ²	36.53±242	–	–	–	–
Length of stay (means)					
€	4363.51±2476.0	4914.53±2517.0	0.46	3896.33–5381.71	0.89
€/cm ²	189.44±118.4	226.47±124.4	0.31	171.74–244.17	0.84
Total healthcare cost					
€	5672.14±2900.1	6369.44±3062.1	0.43	5131.05–6910.53	0.89
€/cm ²	247.0±141.7	288.38±140.0	0.32	225.89–309.50	0.86

Data are expressed as means±standard deviation

^a Significant differences between both groups

^b t test for independent samples

^c Cost ratio=ratio of costs for dermal substitutes group to costs for standard group

hospitalization days ($r=0.68$; $P<0.001$), and complete healing days ($r=0.98$; $P<0.001$). There was not a significant relationship between total cost and age ($r=0.002$; $P=0.9$), lesion number ($r=-0.02$; $P=0.9$), and groups ($r=-0.12$; $P=0.25$).

Discussion

Our results show that patients in dermal substitutes group experienced a generally faster healing process, with engraftment rates compared with the standard group but without any failure due to infective complications. We consider it essential for such results to have an accurate wound bed preparation, as described by TIME scheme, and a careful selection of patients after lesion debridement.

The morbidity of two surgical procedures (in case of DL matrix) is in our opinion balanced by the advantage of a reduced overall hospitalization time, a less invasive procedure, and a considerably lower surgery time needed than the standard group ($P<0.05$), in addition to less surgical revisions needed. Also, the ability to apply dermal substitutes under local anesthesia may be an essential advantage when treating patients unable to receive general anesthesia.

Regarding the complication rate, the most significant difference between the groups was represented by pathological scarring which occurred more frequently in the bioengineered matrix reconstruction group. Despite small group sizes, the results show that the overall cost of management of patients who receive dermal substitutes exhibits a trend to be lower. Significant savings were identified related to surgical costs ($P<0.001$), while hospitalization costs, which contribute most to patient expenses, seem to be reduced but not in such a dramatic way. It is reasonable to hypothesize that identifying patient clusters based on lesion size may lead to identify a range (presumably around 40–60 cm²) where dermal substitute treatment can achieve significant economical advantages. This could be further determined by analyzing trend curves of cost per square centimeter and lesion areas for both groups.

Additional studies are needed to further confirm the results obtained here. We would suggest that larger trials, using multiple centers and randomizing patients to groups would be most advantageous for determining the effectiveness of each intervention approach.

Currently, the excision of traumatized and damaged areas with subsequent flap reconstructions, sometimes combined with dermo-epidermal grafts, are still the most common procedures performed by surgeons [22, 23]. Microsurgical flaps only rarely represent the first line of treatment since they are characterized by long surgical time. Furthermore, the need for proper surgical instruments and the intervention itself presents considerable technical difficulties to the point that the ability of the surgeon appears to be one of the main factors in determining the success of the procedure [24, 25]. Despite great advantages allowed by microsurgical flaps (in terms of

customization for dimension and quality of flap tissue, and the possibility of choosing donor site in areas not directly related to the trauma, thus lowering the risk of presenting damaged vascular vessels), what said above is still sufficient to limit its use to cases where classic pedicle flap treatment is impractical [26, 27].

Myocutaneous or muscular pedicle flaps are instead a reliable technique of simpler execution than microsurgical options: the lesion coverage is reached in the majority of patients without the need for surgical revision. However, disadvantages are related to frequent and potential functional deficits of the donor site and a generally poor cosmetic result (even in donor areas) [28, 29].

Limitations

Our study does not actually include rehabilitation costs due to such a great variety of treatment patterns (depending on patients age, necessity, and will of reaching functional restoration, house location) thus limiting the cost analysis. Additionally, we did not include the cost of anesthesia in our study. As previously mentioned, the sample size was small but it is difficult to recruit an adequate population of 12 as such injuries are relatively uncommon.

Conclusions

The current study suggests that not only clinical but also possible economic advantages in choosing dermal substitutes may exist. Additionally, surgical costs and surgical time are lower with the use of dermal substitutes. In the future, we hope new clinical trials will determine if there truly is an advantage to using dermal substitutes in this population.

Conflict of Interest No funding sources or conflicts of interest were reported for this study.

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