Abstract

Background:

Donor site aesthetic outcome of epidermal graft(EG) against split thickness skin graft(SSG) have yet to be objectively compared. Here, we evaluate the donor site healing using a validated scar assessment tool and digital colorimetric technique which compares colour in a consistent and objective manner.

Methods:

Ten patients (SSG(n=5) and EG(n=5)) were included. Donor site scarring was evaluated using Vancouver Scar Scale(VSS) at Week 6 and Month 3. Colorimetric measurement was performed at Week 3, 6 and Month 3.

Results:

The mean donor site healing time for EG was significantly shorter (EG: 4.6 days (95% c.i. 3.8 to 5.3), SSG: 16.8 days (95% c.i. 13.3 to 20.1)(p=0.003)). The VSS scores of the EG donor site were lower at Week 6 and Month 3(p<0.001). The colour match between the donor site and surrounding skin for EG was better compared to SSG at all time points and was almost identical to their surrounding healthy skin at Month 3.

Conclusions:

This study is the first to objectively measure the clinical appearance of the EG donor site against SSG. EG donor site has faster healing with excellent scarring and good colour match with its surrounding normal skin at all time points compared to SSG.

Introduction

Split thickness skin graft (SSG) remains the most frequently used reconstructive option for coverage of a healthy granulating wound (1). This procedure involves the harvest of the epidermis and part of the dermis, hence creates a second wound at the donor site. Patients may experience donor site discomfort (pain and itching), delayed healing, infection and unsatisfactory cosmetic appearance (2). Several clinical studies have explored different dressings option and techniques to minimise these donor site complications (3-6). Despite demonstrating improvement in clinical outcome, the donor site complications are yet to be overcome.

An emerging option of autologous skin grafting that has potential to overcome the challenges of donor site morbidity is epidermal graft (EG). EG involves harvesting only the epidermal layer of the skin from the donor site by applying continuous negative pressure on normal skin to raise blisters (7-9). The roof of the blister, which is the epidermis, is then excised and transferred onto the wound. As the dermis in the donor site remains untouched, the skin regenerates itself with minimal scar. This procedure is painless as the pain fibres in the dermis are unstimulated, allowing the procedure to be performed in the outpatient setting without administration of anaesthesia (9).

We have previously reported the patient reported outcome measure (PROM) comparing EG and SSG, whereby patients receiving EG reported lower donor site noticeability and higher overall satisfaction compared to SSG (10). Although patient's perspective on the overall treatment outcome has been informed, their perception on the aesthetic outcome may vary between individuals. To date, the donor site aesthetic outcome of EG and SSG have not been objectively compared. Here, we aim to evaluate the clinical outcome of the EG and SSG donor

site healing using a validated scar assessment tool and digital colorimetric technique which compares colour in a consistent and objective manner, hence eliminating variation in human colour perception.

Methods

Patient selection

Ten patients (five who had undergone SSG and five who had undergone EG) were included in this study (Table 1). EG is an established procedure at the trust and patients for this study were selected in a sequential manner from the list of patients referred for SSG and EG at the trust. All patients underwent either of the treatments once their wounds developed healthy granulation tissue with good vascularity. The enrolled patients had skin colour between Fitzpatrick type 1 to 3. The study was conducted at the Royal Free NHS Foundation Trust Hospital London between November 2016 and March 2017. Demographics between the groups were compared with independent t-test using SPSS version 24(IBM, Armonk, NY, USA) with a p value of less than 0.05 was considered significant (Table 1).

EG and SSG harvest technique

EG

This procedure was performed in the outpatient Plastic Surgery dressings clinic using the CelluTome Epidermal Harvesting System(9). Prior to grafting, the wound was cleaned using wound irrigation solution and debrided if necessary. The suction head of the CelluTome Epidermal Harvesting System was applied to the donor site (thigh) for 30-40 minutes to

harvest EG as per protocol(8, 9). The harvested EG was then transferred onto the wound using a non-adhering silicone dressing (Adaptic Touch, Systagenix). The donor site was dressed with Tegaderm (3M). The wound and graft were first checked at day 7.

<u>SSG</u>

This procedure was performed in the operating theatre under general or local anaesthesia. The wound was initially debrided by the treating surgeon in a similar manner to the EG group. Skin was harvested from the thigh using an electric air dermatome, set to cut at the thickness of 8/1000 inch, which was then be meshed by 1:1.5. The wound was grafted and dressed with Adaptic Touch (Systagenix), gauze and Mepore or wool and crepe bandage, or negative pressure wound therapy depending on the site of the graft. The donor site was dressed with Kaltostat (Alginate dressing) with a 2.5cm overlay beyond the wound margins followed by a layer of gauze and secured with Mefix. As per standard clinical practise at the trust, the graft was checked at day 5 and the donor site was first checked at day 14.

Scar quality using Vancouver Scar Scale

Donor site scar was evaluated using the Vancouver Scar Scale (VSS) at Week 6 and 3 Months. Assessment was done by an independent assessor during patient's outpatient dressing clinic appointment. The donor site healing quality was compared using independent t-test.

Images capture

The donor site of each patient was captured in a standardised manner using the LifeViz 3D Camera (Quantificare), which generates high resolution three-dimensional (3D) images. All

images were captured using an in-built flash and standardised settings (shutter speed, aperture, white balance, saturation, colour balance). The camera has an in-built laser that guides the distance from the object to ensure all images were captured at equidistance.

Colorimetric

Colorimetric technique provides standardised measurement that assure consistency and repeatability(11). This technique breaks down colour into three primary components of colour vision as per human eye receptors: red, green, blue. Colorimetric measurement was performed using the donor site images captured at Week 3, Week 6 and Month 3 post grafting. Two patients in the EG group and one patient in the SSG group were missed to follow-up at Month 3. Analysis was performed using ImageJ (http://imagej.nih.gov/ij/). The region of interest that best represents the wound was manually chosen: 3 areas in the donor site, each measuring 50 pixels, that were adjacent to the wound edges were randomly selected. The colours in these selected areas were separated into the 3 primary colours, giving the X-Y-Z coordinates, using the colour histogram function in ImageJ. The mean value for the 3 colours in the 3 areas were calculated and plotted in a 3D graph with 3 axes using OriginPro 2017 Graphing and Analysis software. The difference in colour match between the donor site and surrounding healthy skin for each patient is demonstrated by the distance separating the plots in the graph.

Results

Time to healing

All patients had complete healing of their donor site. The mean donor site healing time for EG was 4.6 days (95 percent c.i. 3.8 to 5.3), significantly shorter compared to the mean donor site healing time for SSG which was 16.8 days (95 percent c.i. 13.3 to 20.1) (log-rank test, p=0.003) (Figure 1). All patients receiving EG did not require further donor site dressing after the first week review. Two of the patients receiving EG reported that the donor site dressing fell off at day 3 and 4 respectively and the wound remained dry with scabs over the harvested sites. The donor sites were left undressed from then onwards. All patients receiving SSG had their first donor site dressing change at day 14 post grafting, with no reported complications such as infection or haematoma.

All patients had complete healing of the wound site. The mean time for wound healing for EG was 8.4 weeks (95 percent c.i. 5.4 to 11.3), while the mean healing time for SSG was 7.2 weeks (95 percent c.i. 3.7 to 10.7) (log-rank test, p=0.415). There were no graft failures.

Scar quality

The VSS score of the EG donor site was lower than SSG, both at Week 6 (0.4 ± 0.0.8 Vs. 4.2 ± 0.7; p<0.001, independent t-test) and at Month 3 (0.2 ± 0.4 Vs. 3.2 ± 0.4; p<0.001, independent t-test).

The donor site of EG was barely visible at Week 6 and Month 3. At Week 6, areas of minimal hypopigmentation or hyperpigmentation were seen over the donor site in some patients which then gradually remodelled to match the surrounding skin. The donor site of all patients

receiving SSG healed well without infection, hypertrophic scarring or keloid formation. The donor sites were seen to be hyperpigmented with increased vascularity at week 6, which then fades over time, although remains visible at Month 3. Figure 2 illustrates the clinical outcome of the donor sites for both treatment groups.

The pliability of skin of all patients receiving EG was similar to the surrounding skin at Week 6 onwards. The SSG donor site was slightly firm at Week 6 but improved with time and all patients had good pliability at Month 3 with constant application of moisturiser on daily basis.

Colorimetric measurement

The colorimetric measurements of the donor site healing correspond with the clinical observation. The difference between the donor site and its surrounding normal skin for both EG and SSG was greatest at Week 3 post grafting and gradually improved to match the surrounding skin, represented by the reduction in the distance between plots in Figure 3. The difference between the donor site and its surrounding skin for SSG was greater compared to EG at all time point.

Discussion

Wound reconstruction with autologous skin graft is an important modality for coverage of wounds with healthy granulating bed. SSG has been the primary treatment option, however often requires hospital admission, even as a day case, anaesthesia, and results in donor site morbidity. Several recent publications have highlighted the potential of EG as a viable alternative to SSG that can be performed in the outpatient setting, benefitting patients with

multiple comorbidities and in resource poor settings (9, 12, 13). This could particularly benefit elderly patients as it does not require anaesthesia and avoids complication of bed rest, maintaining patient's independence and quality of life.

This study is the first to objectively measure the clinical appearance of the EG donor site against SSG. Besides using a standard scar assessment tool, we also adopted a highly objective technique to compare the colour match of the donor site with its surrounding healthy skin using the colorimetric evaluation technique. This technique, which is widely used in global manufacturing and processing industry, eliminates variation in colour perception which can vary widely as it can be affected by illumination, surrounding colour, angle of observation and dissimilarity in colour vision between person to person (11). The colorimetric technique provides standardised measurement that assure consistency and accuracy. This technique breaks down colour into three primary components of colour vision as per human eye receptors. All images that were used for the colorimetric assessment were captured under standardised conditions and were digitally analysed to ensure precise and reproducible results. The colorimetric measurement correlates with clinical appearance of the donor site, further emphasising the reliability of this technique.

We found that the EG donor sites have excellent scarring and good colour match with its surrounding normal skin. They displayed similar pigmentation, pliability and vascularity to the surrounding skin. The donor sites were merely visible at Month 3 post grafting in all patients, and some even from Week 6 onwards. In comparison, the donor site of SSG was clearly visible at Month 3 in all patients. Additionally, besides the lower donor site morbidity, the donor site healing time of EG is also significantly shorter compared to SSG. The rapid healing and aesthetically superior outcome of the EG donor site is due to the superficial nature of the

harvested skin and the design of the harvester which harvests 128 small islands of EG (micrographs) with a 2mm gap(8). This enables keratinocytes and melanocytes to proliferate and migrate from the healthy surrounding skin to heal the donor site in a rapid manner. Furthermore, as the hair follicles at the donor site not affected by the superficial nature of the harvest, the stem cells within them are also able to contribute to the rapid healing of the donor site.

The lower donor site morbidity and faster healing time is likely the main contributing factor to the high satisfaction among patient undergoing this treatment, as previously reported (10). Besides that, the rapid donor site healing could potentially reduce cost and usage of healthcare resources as it only requires a single application of a simple film dressing. This could potentially lead to major positive implication to clinical practise as SSG often results in donor site which requires meticulous wound management (14). Furthermore, the optimal choice of donor site dressing for SSG is still debatable as highlighted in a systematic review which reported that current evidence is weak to suggest the best dressing for SSG donor site (15). However, a formal cost analysis study is required to formally evaluate and compare the cost involved for both EG and SSG to determine if this treatment could reduce total treatment cost for patients.

The ability of the EG donor site to heal with minimal or no donor site morbidity brings about the possibility of re-grafting the wound should patients suffer from delayed wound healing or if the wound gets infected after the initial grafting. Several histological studies performed using healthy donors have confirmed that the EG is harvested down to the basal membrane, hence the entire ultra-structure of the epidermis remains intact (7). Hence the EG consist of multi-layered keratinocytes in which a variety of other cell types with specialised functions

are embedded, such as the melanin pigment-producing melanocytes, the immune-competent Langerhans cells and the neuroendocrine Merkel cell, while its basal layer contains epidermal stem cells (16). Along with the cells, EG have been shown to secrete several growth factors and cytokines which includes vascular endothelial growth factor(VEGF), tumour growth factor-α(TGF-α), platelet-derived growth factors(PDGF), hepatocyte growth factor and granulocyte colony-stimulating factor (7, 16). These growth factors are known to modulate wound-healing response and can stimulate the endogenous process of wound healing (7). Hence, this creates the possibility of a different approach to deal with chronic non-healing wounds as the repeated grafting could be a method to repetitively deposit cytokines and growth factors that are desirable to promote healing, thus behaving more like a bioengineered skin. Although this is an exciting possibility, the cost effectiveness of repeated grafting needs to be assessed.

Study limitation

This study is an observational study, therefore prone to selection bias. For this study, patients receiving treatment within the standard clinical pathway were randomly selected in a sequential manner, identified from routine referrals. Besides that, despite demonstrating consistent results between patients within the same group, the sample size is small and does not take into consideration of patients from a broad range of Fitzpatrick skin type, especially patients with pigmented skin. A larger prospective randomised controlled trial is therefore necessary to address these limitations and to provide high level evidence to guide clinical practise.

Conclusion

This study provides an objective comparison on the EG and SSG donor site outcome which shows that the EG donor site has rapid healing and better colour match compared to SSG at all time points (Week 3, Week 6 and Month 3). EG is an autologous skin grafting option which can be performed in the outpatient setting with potentially minimal donor site morbidity. This study also demonstrates the potential to perform colorimetric measurement to objectively evaluate healing outcome. However, a larger study with higher level of evidence is necessary to further substantiate the finding of this study.

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Tables

Table 1: Demographics of patients included in the study

		EG (n=5)	SSG(n=5)	p value
Age: Average (range)		60 (48-82)	67.8 (44-92)	0.451
Male: Female		2:3	2:3	
Aetiology of wound				
	Wound dehiscence	4	2	
	Surgical excision	1	1	
	Pretibial laceration		2	
Duration of wound				
	Acute (<3 months)	2	4	
	Chronic (≥3 months)	3	1	
Location of wound				
	Leg	2	3	
	Abdomen	1	1	
	Breast	1		

	Back	1	
	Groin		1	
Average wound size (mean cm²)	13.7 ± 7.4	28.6 ± 23.7	0.215
Average donor site size (mean cm²)	25.0	39.7 ± 16.2	0.078

Figures

Figure 1: Kaplan Meier plot of time for complete donor site healing
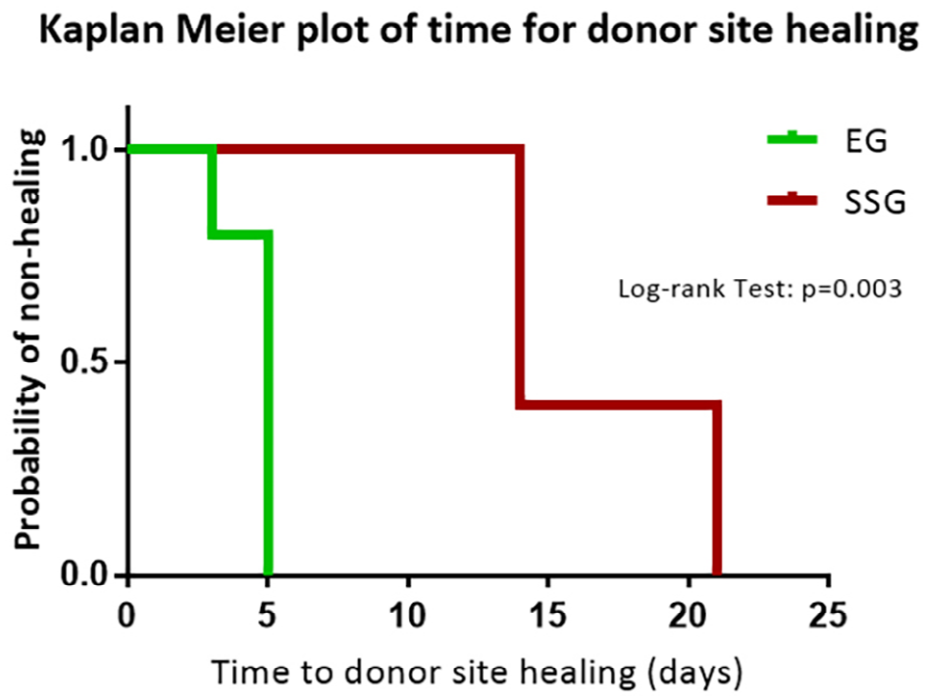

Kaplan Meier plot of time for donor site healing

Figure 2: Clinical photographs of the EG and SSG donor site wounds at Week 3, Week 6 and Month 3. The black arrows point to the donor site wounds.
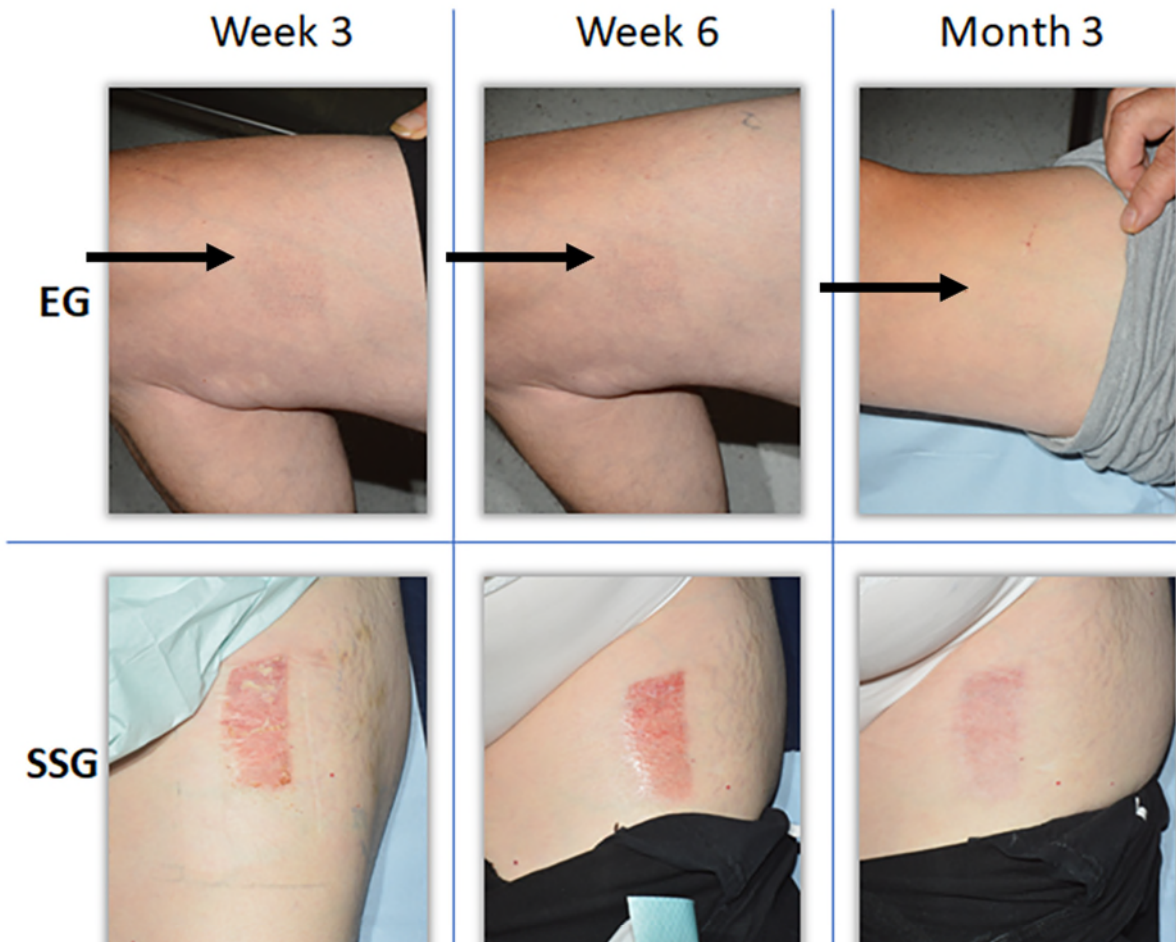
Figure 3: Colorimetric measurement of the donor site and surrounding healthy. The black lines join the donor site and surrounding skin colorimetric measurement for the same patient. The length of the black lines represents the difference in colorimetric measurement between the donor site and surrounding skin for each patient. The colour match between the donor site and surrounding skin for EG was noted to be better compared to SSG at all time points. The donor site of EG was almost identical to their surrounding healthy skin at Month 3.