

Recent Updates on the Management of Split-thickness Skin Graft Donor Sites

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Background: This article is a narrative review of split-thickness skin graft donor site (STSG-DS) management since the international guidelines were created in 2018. Although many new interventions have been developed, there is a lack of quality, multicentered clinical trials to produce updated evidence-based recommendations.

Methods: Electronic databases, including Google Scholar, Web of Science, Medline, and PubMed, were searched by two independent researchers for literature regarding STSG-DS management published from 2018 through 2022, using specific terms in the text, title, and abstract. The primary endpoint assessed was STSG-DS healing, as measured by wound epithelialization.

Results: Thirty-one articles were selected, including three systemic review/meta-analyses, five case series, 14 randomized controlled clinical trials, six observational studies, and three nonrandomized trials. Novel interventions for STSG-DS management included in this article describe applications of human amniotic membranes, acellular dermal matrices, cell suspensions and growth factors, biomaterials, electromagnetic radiation, and natural products.

Conclusion: Various interventions have shown promise for STSG-DS management since the creation of the 2018 international guidelines; however, studies with more standardized protocols and endpoints are needed to produce up-to-date, evidence-based recommendations and improve outcomes for patients undergoing split-thickness skin grafting. (*Plast Reconstr Surg Glob Open* 2024; 12:e6174; doi: 10.1097/GOX.0000000000006174; Published online 18 September 2024.)

INTRODUCTION

Currently, there is no clinical consensus on split-thickness skin graft donor site (STSG-DS) management, and new interventions are warranted.^{1,2} In 2018, a group of global experts proposed the use of six primary dressing choices: foam, hydrocolloid, silicone, alginate, nonadherent/tulle, and absorbent acrylic; however, STSG-DSs remain a source of significant patient morbidity.³ Novel

interventions have since been developed; however, many of the studies conducted are underpowered or low on the evidence-based pyramid. The objective of this review was to provide a current snapshot of emerging interventions published between 2018 and 2022, provide example data, and highlight pros and cons of each method.

METHODS

Electronic databases, including Medline, Web of Science, the Cochrane Library, and PubMed, were systematically searched by two independent researchers for literature regarding STSG-DS management published from 2018 to 2022. The key phrases “skin graft donor site” OR “split-thickness skin graft donor site” were searched in all fields. Manual searches of reference lists were also conducted in Google Scholar to identify additional studies. Inclusion criteria were studies of any experimental design involving STSG-DS management published on all patient age groups and in all languages between 2018

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and 2022. We excluded grafts that were not split thickness or donor tissues other than skin. Ultimately, 31 citations were chosen, which are representative of the 2018–2022 body of literature. As this article is intended to provide a survey of emerging therapies (despite the level of evidence), individual study quality assessment was deferred. The primary endpoint assessed was STSG-DS healing, as measured by wound epithelialization. Secondary endpoints included time to wound epithelialization, pain, cost of dressing and wound management, ease of use, cosmetic appearance and scar formation, and complication type and rate.

RESULTS

Human Amniotic Membranes

In a double-blind phase 1 randomized clinical trial (RCT), Momeni et al showed that human amniotic membranes (HAMs) significantly increased the reepithelialization rate of STSG-DSs by approximately day 4 compared with petroleum-impregnated gauze. Although pain intensity scores were similar across treatment groups in the immediate postoperative period, scores in the HAM-treated group were significantly decreased at postoperative days (PODs) 8, 11, and 14.⁴ A subsequent double-blind RCT showed better pain reduction and epithelialization in HAM- versus petrolatum gauze-treated donor sites at day 10, with no increase in healing rates.⁵ Interestingly, another RCT showed that HAMs induced statistically equivalent results in terms of pain and reepithelialization compared with silicon.⁶

In 2020, two SMRAs concluded that HAM-treated STSG-DSs had decreased healing times; however, the conclusions drawn regarding pain were incongruent. The prior study included 157 patients and found a significant decrease in healing time with an increased proportion of healed HAM-treated STSG-DSs by day 12 versus gauze, with a concomitant decrease in pain and pruritus.⁷ A follow-up SMRA included an additional 62 patients in the analysis and observed no benefit in pain reduction or infection rates.⁸ Key findings using HAM-based interventions are summarized in [Table 1](#).

Acellular Dermal Matrices

Acellular dermal matrices (ADMs) are derived from both human and nonhuman sources, although few studies have examined the role of human ADMs in STSG-DS management. In 2019, a prospective comparative study with 52 patients found that fish-derived collagen (Kerecis) significantly decreased STSG-DS healing time by 2.4 days versus cow-derived collagen (ProHeal).⁹ A 2019 case series reported that piscine ADM-treated STSG-DSs had decreased healing times compared with previously published studies using foam, silver, alginate, and silicone dressings.¹⁰ One prospective cohort study with 21 subjects found that fish ADM decreased healing times, pain levels, and local infection rates compared with paraffin gauze.¹¹ Key findings using ADM-based interventions are summarized in [Table 2](#).

Takeaways

Question: What is new in the management of skin transplant donor sites?

Findings: There are a variety of novel dressings for skin donor transplant sites that show promise; however, there is a paucity of high-powered studies supporting best practices in 2023.

Meaning: A variety of novel dressings are in development for the care of skin transplant donor sites, but more high-powered clinical studies are needed to support best practices in 2023.

Autologous Cell Suspensions and Insulin

Autologous cell suspensions (ASCs) have shown efficacy in STSG-DS management. An SMRA from 2021 found that ASCs reduced time to reepithelialization in adult STSG-DSs compared with standard of care.¹² Foster et al showed that ASCs could decrease healing time following multiple STSG harvests, with the resulting scars displaying improved cosmesis.¹³ Decreased healing time and increased Patient and Observer Scar Assessment Scale scores were observed in a small, nonrandomized trial using a similar technique involving treatment of STSG-DSs with minced residual STSGs.¹⁴

Platelet-rich plasma and fibrin (PRF) have been shown to shorten healing time and reduce pain scores without significant postoperative complications.^{15–18} However, a lack of standardized platelet-rich plasma/PRF production and reporting techniques has precluded its widespread clinical utility.¹⁹ Interestingly, local administration of insulin within the donor wound bed has been shown to significantly increase both the area and rate of epithelialization compared with vehicle.²⁰ Key findings using ACS- and insulin-based interventions are summarized in Supplemental Digital Content 1. (See [table, Supplemental Digital Content 1](#), which displays key findings from studies using ACS- and growth factor-based approaches to decrease STSG donor site morbidity. <http://links.lww.com/PRSGO/D513>.)

Nanomaterials, Polymers, and Silicon

In a randomized prospective trial of 41 patients, Haik et al²¹ showed that Jelonet, an electrospun nanofibrous polymer-based matrix, demonstrated significantly lower POD 1 Draize dermal irritation scores compared with paraffin gauze dressings (Jelonet) or silicone foam dressing (Biatain); time to reepithelialization, adverse events, pain, and infection rates were statistically equivalent between groups. In a clinical study from Finland, nanofibrillar cellulose was shown to perform similarly to a related but more expensive polylactide-based copolymer in terms of pain, wound healing time, Patient and Observer Scar Assessment Scale scoring, and moisture retention.²²

Chowdhry et al²³ reported faster donor site epithelialization times and fewer office visits with the use of oxidized regenerated cellulose collagen/silver-oxidized regenerated cellulose dressing compared with petrolatum-impregnated gauze dressings in a

Table 1. Key Findings from Studies Using HAM-based Approaches to Decrease STSG Donor Site Morbidity

Study	Study Design	Outcomes				Control	Comment
		Reepithelialization	Pain	Adverse Events	Wound Healing Time		
Abul et al ⁷	Systemic review and meta-analysis (N = 157)	OR 6.12, CI 1.45–25.77, <i>P</i> = 0.01	Decreased in HAM-treated groups (different scales used)	OR = 0.48, CI = 0.13 to 1.77, <i>P</i> = 0.27	MD = –3.62 d, CI –4.95 to –2.29, <i>P</i> < 0.0001	–Impregnated gauze –Paraffin gauze –Chlorhexidine-impregnated paraffin and cotton gauze –PU foam and foil	
Momeni et al ⁴	Randomized double-blind phase I clinical trial (N = 10)	HAM: mean 11.3 ± 2.9 d to closure Control: mean 14.8 ± 1.6 days to closure	Significantly reduced on days 8, 11 and 14, <i>P</i> < 0.05	No significant difference between groups	Significantly reduced wound size at days 4, 8, and 11, <i>P</i> < 0.05	Vaseline-impregnated gauze	No increased benefit from HAMs seeded with fetal fibroblasts
Nouri et al ⁶	Randomized controlled clinical trial (N = 20)	aHAM: 2 ± 1.41* HAM: 2 ± 1 Control: 2.5 ± 0.93 <i>P</i> = 0.573 (at day 12)	No differences vs. control at days 4, 8, and 12	N/A	N/A	Mepitel	No differences versus control VSS score at 3 and 6 mo post-operatively
Vaheb et al ⁵	Double-blind randomized controlled clinical trial (N = 35)	HAM: –Investigator 1: 1.40 ± 0.88† –Investigator 2: 0.91 ± 0.85 Control: –Investigator 1: 1.62 ± 0.59 –Investigator 2: 1.22 ± 0.84 <i>P</i> ₁₁ = 0.009, <i>P</i> ₁₂ = 0.003 (at day 10)	Significantly reduced on days 10, 20, and 30, <i>P</i> < 0.001	N/A	No significant difference in wound healing time or % healed at days 10, 20, and 30	Petrolatum gauze	
Liang et al ⁸	Systemic review and meta-analysis (N = 219)	RR 1.61, CI 0.047–5.46; <i>P</i> < 0.00001	No statistical difference in sensation of pain (<i>P</i> > 0.05)	RR of infection = 0.66	MD = –3.87 days, CI –4.39 to –3.35, <i>P</i> < 0.00001	Multiple	

*4; >90% reepithelialization.

3: 70%–90% reepithelialization.

2: 30%–70% reepithelialization.

1: <30% reepithelialization.

†Scored from 0 (none) to 3 (thick, complete surface) epithelialization.

OR, odds ratio; CI, confidence interval; HAM, human amniotic membrane; aHAM, acellularized human amniotic membrane; MD, mean difference; PU, polyurethane; VSS, Vancouver scar scale; *P*₁₁, *P* value from investigator 1; *P*₁₂, *P* value from investigator 2; RR: P relative risk; N/A, not applicable.

retrospective analysis of 20 patients. Similarly, Alberto and colleagues used a comparable dressing on donor sites in a case series of 39 patients. In their cohort, 89.7% of patients received at least prophylactic anticoagulation; however, the authors reported no bleeding complications, and the dressings could be removed without causing pain in 64.1% of patients.²⁴ However, Hecker et al²⁵ found no differences in healing time between nanocellulose dressing and silver-impregnated or ibuprofen-containing foams.

Povidone-iodine-impregnated polyurethane dressing (Betafoam) induced significantly faster healing times while requiring fewer dressing changes compared with petrolatum-impregnated gauze and the hydrocellular foam dressing (Allevyn) with equivalent complication rates.²⁶ A silver-containing carboxymethylcellulose (Ag-CMC) hydrofiber (AQUACEL) has also been shown

to achieve complete donor site epithelialization in pediatric patients with a single postoperative application.²⁷ Recently, a retrospective analysis of 30 patients showed that inclusion of a high-density polyethylene polymer under bismuth or petroleum gauze resulted in no significant changes in STSG-DS pain or healing time.²⁸ Silicon dressings have been scarcely studied for STSG-DS management but have shown reduced pain scores compared with petrolatum gauze.²⁹

Chitosan or Animal-derived Treatments

Chitosan is a naturally occurring polysaccharide that can be extracted from crustacean shells. Uke et al³⁰ published a case series of 114 patients with STSG-DSs treated with chitosan-based dressings and observed an infection rate of 7%, a bleed-through rate of 1.8%, and a reapplication rate of 9.6%.

Table 2. Key Findings from Studies Using ADM-based Approaches to Decrease STSG Donor Site Morbidity

Study	Study Design	Outcomes				Control	Comment
		Reepithelialization	Pain	Adverse Events	Wound Healing Time		
YOON et al, 2022 ⁹	Prospective, comparative, single-center (N = 52)	N/A	N/A	N/A	Group 1: ASM: 9.1 ± 1.0 days Control: 11.9 ± 1.4 days Group 2: ASM: 10.7 ± 1.5 days Control: 13.1 ± 1.4 days	Group 1: nontreatment Group 2: ProHeal	-Fish ADM (Ker-ecis) -Study contained various in vitro comparisons as well
Alam et al, 2019 ¹⁰	Case series (N = 10)	90% and 100% epithelialization reached at an average of 8.5 (range 7–13) and 11.5 (range 10–16) d, respectively	2.3* (range 1–4) at day 7	No infection or adverse reaction noted	N/A	N/A	-Fish ADM -Quality of healing judged to be good in all cases
Badois et al, 2019 ¹¹	Prospective, comparative, before-after cohort (N = 21)	N/A	POD 5: ADM: 0 VAS scores of ≥ 3 Control: 4 VAS scores of ≥ 3, P = 0.034	ADM infection rate: 0% Control infection rate: 60%, P = 0.0039	ADM: 31.5 ± 24.7 d Control: 67.9 ± 66.2 days, P = 0.126	Paraffin gauze	-Fish ADM

*Verbal rating score of 0–10.

N/A, not applicable; VAS, visual analog scale.

Plant-derived treatments

An RCT and systematic review in 2018 found that aloe vera (AV) gel-impregnated gauze was superior to glycerin placebo in terms of time to complete epithelialization; however, there were no pain control benefits.³¹ A follow-up study in 2020 showed that, in combination with honey and peppermint, AV gel significantly decreased STSG-DS wound erythema compared with petroleum jelly while having no effect on the rates of wound healing, pain, pruritus, or patient discomfort.³² Similarly, a cream containing derivatives from the *Zataria multiflora* plant accelerated donor site wound healing and reepithelialization rates compared with petrolatum ointment in a prospective, randomized, placebo-controlled clinical study in 2022.³³

Photobiomodulation

A recent case series in 2021 comparing the effects of a 660-nanometer light-emitting diode on skin graft donor sites showed a significant reduction in pain on POD 5 with no changes to reepithelialization time, wound area, or wound quality.³⁴ Key findings using nanotechnology-, polymer-, AV-, silicon-, and photobiomodulation-based interventions are summarized in Supplemental Digital Content 2, and the pros and cons of each intervention discussed are displayed in Figures 1 and 2. (See table, Supplemental Digital Content 2, which displays key findings from studies using nanotechnology-, polymer-, AV-, and photobiomodulation-based approaches to decrease STSG-DS morbidity. <http://links.lww.com/PRSGO/D514>.)

DISCUSSION

Paraffin gauze is widely used in STSG-DS management but is associated with significant adverse events.³⁵

Although prior studies have shown that moist dressings are largely superior to nonmoist dressings, newer treatment modalities with unique tissue-regenerative properties have not been adequately evaluated in terms of healing time, pain, cost, cosmesis, efficacy, and complication rates.³⁶ In this narrative review, we have identified multiple interventions for STSG-DS management published after the establishment of the 2018 international guidelines. Many studies reviewed herein have produced encouraging data but are underpowered or ungeneralizable. To produce updated guidelines with improved reliability and clinical relevance, data pools need to be significantly expanded and study populations stratified by factors well known to impact wound healing (eg, comorbid conditions such as advanced age, smoking, and diabetes). Moving forward, we recommend RCTs targeting similar patient populations with utilization of standardized treatment protocols, graft harvest techniques, and outcome measures. Our summary of emerging STSG-DS treatment strategies (including HAMS, acellular skin matrices, ASCs, growth factors, nanomaterials, polymers, silicon, AV, and photobiomodulation) provides a current snapshot of the field and serves as a foundation to trigger future research.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.


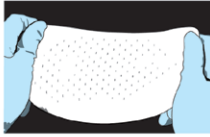
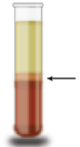
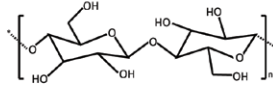
Material	Pros	Cons
HAM 	<ul style="list-style-type: none"> - Utility in specialized mucosal and ocular surfaces - Decreases healing time - Decreases pain 	<ul style="list-style-type: none"> - High cost - Ethical challenges - Production bottleneck
ADM 	<ul style="list-style-type: none"> - Readily available - Long shelf life - Decreases healing time 	<ul style="list-style-type: none"> - Xenogeneic derivations can transmit disease
CGF 	<ul style="list-style-type: none"> - Covers large deficits with small harvests - Decreases healing time - Decreases pain 	<ul style="list-style-type: none"> - Requires additional tissue harvest
NMP 	<ul style="list-style-type: none"> - Easy to manufacture - Require fewer dressing changes - Decreases healing time - Decreases pain 	<ul style="list-style-type: none"> - Variable long-term stability - Unknown long-term safety profile

Fig. 1. Summary table of key findings with illustrations. CGF, autologous cell suspensions and growth factors; NMP, nanomaterials and polymers.





Material	Pros	Cons
SCN 	<ul style="list-style-type: none"> - Decreases pain - Decreases wound bed stripping 	<ul style="list-style-type: none"> - High cost
ADT 	<ul style="list-style-type: none"> - Decreases healing time - Hemostatic properties 	<ul style="list-style-type: none"> - Poor solubility at physiological pH - Poor water retention - Low mechanical resistance
PDT 	<ul style="list-style-type: none"> - Decreases healing time - Decreases wound erythema 	<ul style="list-style-type: none"> - Must use caution in patients with plant allergies
PBM 	<ul style="list-style-type: none"> - Decreases pain - High safety profile 	<ul style="list-style-type: none"> - Large variations in irradiation protocols

Fig. 2. Summary table of key findings with illustrations. SCN, silicon; ADT, chitosan or animal-derived treatments; PDT, plant-derived treatments; PBM, photobiomodulation.

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