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To Glue or Not to Glue? Analysis of Fibrin Glue for Split-thickness Skin Graft Fixation

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Background: Split-thickness skin grafting (STSG) is a commonly used tool in the plastic surgeon's reconstructive armamentarium. Fibrin glue (FG) consists of a combination of clotting factors and thrombin whose key properties include adherence and hemostasis. This preliminary study aimed to assess clinical outcomes and cost of FG for STSG fixation in a general wound reconstruction.

Methods: A retrospective review was conducted in all patients undergoing STSG placement by a single surgeon (JPF) from January 2016 to March 2018. Twenty patients were identified and matched by wound location and wound size. Patients were then divided into 2 groups based on the method of STSG fixation: FG (n = 10) or suture only (SO) (n = 10).

Results: In patients with FG fixation, we observed trends of decreased adjusted operative times (34.9 versus 49.4 minutes, $P = 0.612$), a similar length of stay (2.8 versus 3.5 days, $P = 0.306$), and liberation from the use of negative pressure wound therapy (0 versus 10 wounds, $P < 0.0001$). There were no observed differences between the 2 groups in terms of graft-related complications at 180 days (1 complication FG versus 0 complications SO). Time to 100% graft take was also not different (20.2 versus 29.4 days, $P = 0.405$). Additionally, total direct cost ($16,542 FG versus $24,266 SO; $P = 0.545$) and total charges ($120,336 FG versus $183,750 SO; $P = 0.496$) were not statistically different between the FG and SO groups.

Conclusions: In this preliminary comparative assessment, FG for STSG fixation has shown no difference in clinical outcomes to SO fixation, trends of decreased operative time, and afforded complete liberation from negative pressure wound therapy dressings. *(Plast Reconstr Surg Glob Open 2019;7:e2187; doi: 10.1097/GOX.0000000000002187; Published online 16 May 2019.)*

BACKGROUND

The treatment of acute and chronic wounds continues to serve as a challenge for both physicians and healthcare providers. If these wounds exist for prolonged periods of time, they can cause disability and decreased quality of life for patients.[1–3] The use of split-thickness skin grafts (STSGs) remains an effective technique for wound coverage and is commonly performed by plastic surgeons.[3] STSGs play a key role in establishing wound re-epithelization and serve as an essential rung in the plastic surgeon's reconstructive.[4]

Traditionally, skin grafts are fixated to the recipient donor site using staples or sutures to permit appropriate adherence through mechanical affixation to the surrounding soft tissue.[5] Negative pressure wound therapy (NPWT) and bolster dressings have also emerged as effective adjuncts to optimize graft take and prevent graft shearing during the early stages of healing.[6,7] Although these methods have demonstrated reliable results, various clinical and administrative considerations must be made.[5] Furthermore, adjunctive wound vacuum-assisted closure (VAC) application requires significant health system resources, both administratively and clinically.[8] NPWT system procurement is reliant upon insurance authorization, documentation, and multidisciplinary coordination for directed patient care, while also initiating the potentiality

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of postoperative issues, such as VAC malfunction. Conventional approaches, such as the use of staples and suture, for the fixation of STSG can be time consuming and often constitutes the most tedious part of the operation. These techniques can create difficulties in securing grafts over large, complex, defects and causing increased postoperative pain and numerous office visits for staple removal.

Fibrin glue (FG), such as Tisseel (TISSEEL: Baxter Healthcare Corp, Deerfield, Ill.), consists of a combination of clotting proteins and thrombin, which when applied, mimics the terminal end of the clotting cascade, thus promoting hemostasis and adherence.[9] FG has been increasing in its utilization within a wide variety of surgical subspecialties.[10,11] Much of the emphasis regarding applications of FG within the realm of surgery, particularly in plastic surgery, has leveraged its hemostatic and adherence properties.[11]

Although the use of FG has reported successful outcomes in other areas of reconstructive surgery, current literature is lacking on the use of FG for STSG fixation, specifically in the nonburn patient population. The purpose of this pilot study was to assess the clinical and cost effectiveness of FG for STSG fixation by comparing wound healing outcomes to traditional, suture only (SO), fixation methods in a general wound reconstruction population.

METHODS

Study Design and Patient Selection

A retrospective comparative cohort study was conducted to analyze wound healing outcomes, operative time, length of stay, and costs associated with the use of FG for STSG fixation. This study was reviewed and approved by the Institutional Review Board of the University of Pennsylvania (protocol # 829882). All patients who received an STSG by the senior author (JPF) between January 1, 2016, and March 1, 2018, were retrospectively identified and reviewed. Inclusion criteria consisted of patients of at least 18 years old and who underwent wound coverage with an STSG through either SO fixation or FG fixation. These patients were then separated based on the type of STSG fixation (SO versus FG) and matched based on wound size and wound location.

Overall, 20 patients underwent STSG placement by the senior author (JPF) and were included in the study, 10 of whom had undergone STSG fixation with FG. A comparison group consisting of the additional 10 patients underwent SO fixation and were then matched to the FG cohort based on wound location and wound size, in which all wounds had a minimum size of 175 cm^2. Tisseel (TISSEEL) FG was utilized in all experimental cases for the FG group.

Demographic information was collected for all patients, including sex, age, body mass index, history of smoking, location of wound, and comorbidities such as peripheral vascular disease, hypertension, and diabetes mellitus. Additionally, perioperative factors such as wound size, wound etiology, wound-adjusted operative time, use of NPWT, wound age at the time of STSG placement (≥60 days), and number of operative debridements before engraftment were collected. Finally, postoperative outcomes were analyzed at 180 days post-STSG fixation, including time to STSG healing and graft complications.

Outcomes and Data Analysis

Primary study end points were graft take assessed at 180 days of post-STSG placement and STSG-related complications, defined as graft failure, seroma, and surgical site infection (SSI). Secondary outcomes included wound-adjusted operative times, length of hospital stay, time to 100% graft take, postoperative wound VAC use, and costs associated with the skin graft procedure. Time to 100% graft take was calculated from the day of the STSG procedure to the date of complete healing, determined at a postoperative clinic visit. Wound-adjusted operative time was determined by dividing the case length by the number of wounds receiving an STSG, to examine the time required to affix each graft. Operative times were adjusted based on the number of wounds patients had because some patients received STSGs on more than 1 wound.

The University of Pennsylvania's Department of Finance provided financial data for the index STSG procedure and any additional admissions or reoperations related to the index procedure, within 180 days of post-STSG application. For these encounters, total cost and total charges were collected. Descriptive statistics was conducted for patient demographics, wound characteristics, and postgraft outcomes. Univariate analysis using the Wilcoxon rank sum test and the Fisher's exact test was performed where appropriate. A *P*-value of less than 0.05 was defined as being statistically significant. All statistical analyses were performed using STATA (*STATA Statistical Software: Release 15*; StataCorp LLC, College Station, Tex.).

Operative Technique

After introducing FG into his practice for STSG use on August 30, 2017, the senior author has used this fixation technique in the majority of his STSG cases. This operative technique is described schematically in Figure 1. All cases began with standard wound bed preparation consisting of debridement, irrigation, and hemostasis. An appropriately sized STSG is then harvested from a suitable donor site with the dermatome blade set to 11–13/1,000 inches. The graft is meshed 1.5:1 to optimize coverage and is cut to fit appropriately in the wound bed. The prepped wound bed is sprayed using a CO_2-based sprayer system with a thin layer of FG to cover the wound bed in its entirety. In each case, approximately 4–6 cm^3 of FG is used on the wound beds; however, a greater volume is often used for larger wounds. The graft is then promptly and carefully inset within the wound bed. After insetting the graft, the newly fashioned graft is then sprayed with FG to ensure complete graft fixation. After allowing 2–3 minutes for the FG to dry, wound dressings are applied, which consists of using bacitracin, ADAPTIC (Acelity L.P. Inc., San Antonio, Tex.), abdominal gauze pads pads, and Kerlix sterile gauze, and gently covered with an ACE wrap (3M; ACE, Maplewood, Minn.). Additional FG (2–6 cm^3) is used at the STSG donor site to improve hemostasis and reduce postoperative pain.

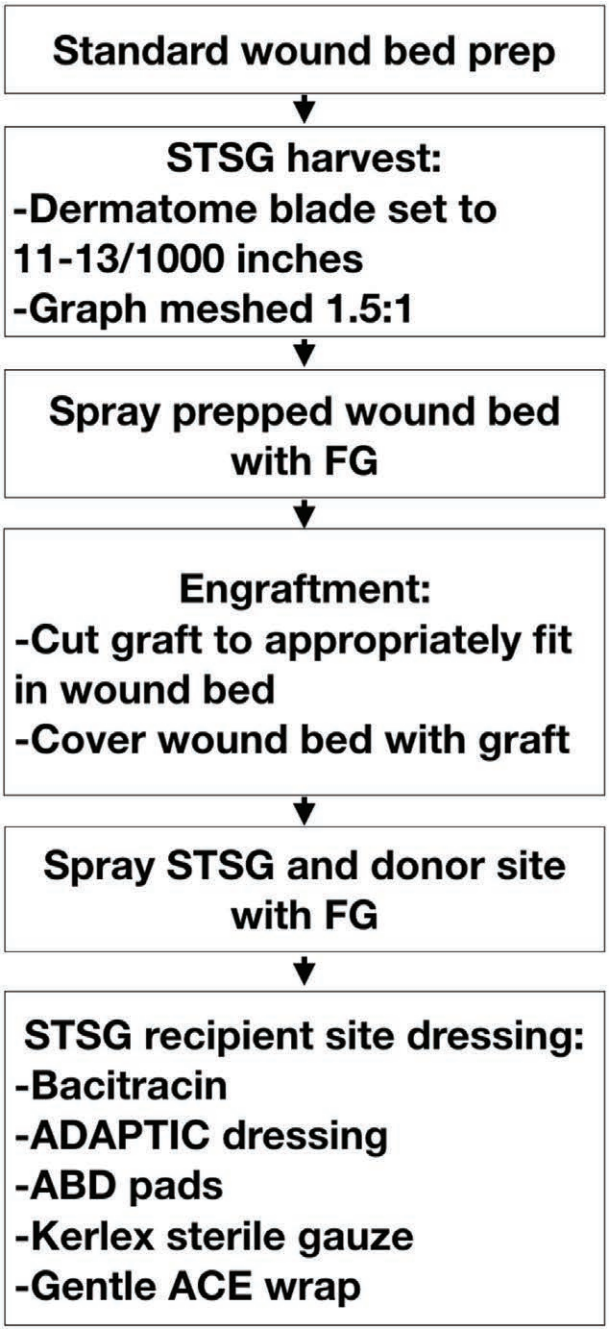

Fig. 1. Flowchart summarizing intraoperative approach for the application of FG to STSG recipient site.

RESULTS

Twenty patients were selected based on skin graft fixation method (FG or SO), wound location, and wound size parameters. Ten patients with 18 wounds receiving FG fixation were compared with 10 patients with 11 wounds receiving SO fixation. Detailed patient demographics and wound characteristics, including healing outcomes, are outlined for each patient in Table 1 (FG cohort) and Table 2 (SO cohort). Of note, 4 patients who underwent FG fixation and 1 patient in the SO group were treated for multiple wounds, which can be attributable to the etiology of their respective wounds. Overall, groups were similar with no significant differences in sex, age, body mass index, presence of peripheral vascular disease, history of necrotizing fasciitis, and history of smoking (Table 3). However, the incidence of hypertension was higher in the SO group, although not statistically significant [2 (20%) FG versus 7 (70%) SO, $P = 0.0698$]. The majority of wounds were confined to the lower extremity (80% FG, 80% SO), with 2 patients in each group having a wound located on the scalp and the perineum.

Wound characteristics for both cohorts are delineated in Table 4, further highlighting a lack of significant differences in average wound size ($P = 0.857$), average wound age greater than 60 days ($P = 0.663$), and number of preoperative debridements ($P = 0.374$). Additionally, wound location and wound type can be appreciated for similarities in anatomic location and etiology (Table 4). A comparison of perioperative and postoperative outcomes for the FG and SO groups is expressed in Table 5. Time to 100% graft take (20.2 days FG versus 29.4 days SO, $P = 0.405$), wound-adjusted operative time (34.9 versus 49.4 minutes, $P = 0.0612$), and length of hospital stay (2.8 versus 3.5 days, $P = 0.306$) were both lower in the FG cohort, although not statistically significant. Of the 11 patients who underwent suture-based STSG fixation, 10 patients received postoperative wound VAC treatment, whereas no patients with FG fixation received wound VAC placement ($P < 0.0001$). Average time to 100% graft take was 20.2 and 29.4 days ($P = 0.170$) for the FG and SO groups, respectively.

Cost data are summarized in Table 6, in regard to total charges and total direct cost for all patients. Average total charges for the FG and SO groups were $120,336 and $183,750 ($P = 0.496$), respectively. Average total direct costs were $16,542 and $24,266 ($P = 0.545$) for the FG and SO groups, respectively.

DISCUSSION

The key properties of FG, hemostasis and adherence, have the potential to play a critical role in plastic and reconstructive surgery, particularly with respect to the success of skin grafting. Graft take is directly dependent on underlying hemostasis to prevent hematoma formation and sufficient graft fixation, to ensure direct contact with the underlying wound bed during the inosculation phase. The results from this preliminary study show no difference in outcomes between FG STSG fixation and SO STSG fixation with the added benefit of liberation from NPWT. Over the past decade, the evidence supporting the use of FG in surgery has increased exponentially in numerous specialties and procedures. In the plastic surgery literature alone, the efficacy of FG has been reported in mesh fixation for abdominal wall reconstruction, demonstrated reduced pain associated with skin graft donor sites, shown to minimize blood loss in facelift surgery and microvascular reconstruction, and as a means to prevent seroma in abdominoplasty, and other body contouring procedures.[12–20]

As other applications of FG are explored, adherence of skin grafts to underlying tissue as a means of promoting

Table 1. Demographic and Clinical Information for Patients Undergoing FG STSG Fixation

	Age (Years)	Race/Ethnicity	Sex	BMI	PVD	History of Smoking	Wound Etiology	Wound Age (Days)	No. Wounds	Wound Location(s)	Wound Size(s) (cm^2)	No. Preoperative Debridements	Time to STSG Healing (Days)
Patient 1	34	White	M	23.0	No	Yes	Surgical site; fasciotomy	45	4	LE; ankle to knee (×4)	342, 370, 252, 442	6	18
Patient 2	52	White	F	20.6	Yes	Yes	Vascular; secondary to sepsis	110	2	LE; ankle to knee (×2)	90, 450	5	27
Patient 3	19	African American	F	22.3	No	No	Traumatic; MVC	3	1	LE; ankle to knee	625	1	26
Patient 4	41	African American	M	30.2	No	Yes	Surgical site; ALT donor site	21	1	LE; knee to hip	527	0	29
Patient 5	61	African American	F	27.1	Yes	No	Vascular ulcer; secondary to CKD	80	1	LE; ankle to knee	330	2	14
Patient 6	25	White	M	23.3	No	No	Vascular ulcer; autoimmune induced	711	1	Scalp	825	5	19
Patient 7	86	White	M	24.3	No	No	Traumatic; ped versus MV	24	1	LE; ankle to knee	1734	1	34
Patient 8	22	White	M	29.0	No	No	Surgical site; Fournier's gangrene	41	1	Perineal	25	2	16
Patient 9	48	African American	M	28.7	No	Yes	Surgical site; fasciotomy	3	4	LE; knee to hip (×2) and ankle to knee (×2)	90, 154, 68, 60	0	12
Patient 10	61	African American	M	25.7	No	Yes	Surgical site; fasciotomy	32	2	LE; ankle to knee (×2)	80, 63	1	7

BMI, body mass index; F, female; M, male; PVD, peripheral vascular disease; CKD, chronic kidney disease; ALT, anterolateral thigh; MVC, motor vehicle crash; LE, lower extremity; MV, motor vehicle.

Table 2. Demographic and Clinical Information for Patients Undergoing SO STSG Fixation

	Age (Years)	Race/Ethnicity	Sex	BMI	PVD	History of Smoking	Wound Etiology	Wound Age (Days)	No. Wounds	Wound Location(s)	Wound Size(s) (cm^2)	No. Preoperative Debridements	Time to STSG Healing (Days)
Patient 1	50	White	M	23.1	No	Yes	Traumatic; electrocution injury	30	1	LE; ankle to knee	360	2	19
Patient 2	56	African American	F	30.2	No	No	Traumatic; AKA	6	1	LE; ankle to knee	390	2	83
Patient 3	81	African American	F	32.3	Yes	Yes	Vascular ulceration	76	1	LE; ankle to knee	256	2	20
Patient 4	21	White	M	34.6	No	Yes	Traumatic; blast injury	16	1	LE; knee to hip	405	2	22
Patient 5	41	African American	F	20.6	No	Yes	Traumatic; dog bite	27	1	LE; knee to thigh	190	4	29
Patient 6	50	White	F	36.4	No	No	Surgical site; fasciotomy	26	2	LE; ankle to knee (×2)	90, 208	1	29
Patient 7	81	White	M	25.2	Yes	Yes	Vascular ulceration	110	1	LE; ankle to knee	220	3	5
Patient 8	57	White	M	33.2	Yes	No	Surgical site; necrotizing fasciitis	42	1	LE; ankle to knee	774	6	26
Patient 9	57	White	M	26.2	No	Yes	Surgical Site; Fournier's gangrene	38	1	Perineal	80	4	55
Patient 10	90	White	M	27.0	No	No	Surgical site; postsquamous cell carcinoma excision	122	1	Scalp	25	1	6

AKA, above knee amputation; BMI, body mass index; F, female; M, male; PVD, peripheral vascular disease.

Table 3. Comparison of Demographic Data Between Fibrin Glue and Suture Only STSG Patients

	Fibrin Glue (n = 10 Patients)	Suture Only (n = 10 Patients)	*P*
No. wounds	18	11	0.111
Females	3 (30)	4 (50)	0.650
Average age (years)	44.7	58.4	0.185
BMI (kg/m^2)	25.4	30.5	0.1303
PVD	2 (20)	3 (30)	—
HTN	2 (20)	7 (70)	0.0698
DM	2 (20)	2 (20)	—
History of smoking	5 (50)	6 (60)	—
History of necrotizing fasciitis	3 (30)	2 (20)	—
Lower extremity wound	8 (80)	8 (80)	—

The values are expressed in n (%).
BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; PVD, peripheral vascular disease.

Table 4. Summary of Wound Characteristics for FG and SO Groups

	FG (n = 18 Wounds)	SO (n = 11 Wounds)	*P*
Average wound size (cm^2)	362.6	272.5	0.857
Wound age >60 days	4 (22.2)	2 (20)	0.663
No. preoperative debridements	2.3	2.7	0.374
Wound location			
Ankle to knee	13 (72)	7 (64)	—
Knee to thigh	3 (17)	2 (18)	—
Scalp	1 (5.5)	1 (9)	—
Perineum	1 (5.5)	1 (9)	—
Wound type			
Surgical site	12 (66.6)	5 (45.5)	—
Vascular wound	4 (22)	2 (18)	—
Traumatic wound	2 (11)	4 (36)	—

The values are expressed in n (%).

Table 5. Comparison of Operative and Postoperative Characteristics

	Fibrin Glue (n = 18 Wounds)	Suture Only (n = 11 Wounds)	*P*
Adjusted operative time (minutes)	34.9	49.4	0.0612
Use of VAC for NPWT post-STSG	0 (0)	10 (90.1)	< 0.0001
Time to 100% graft take (days)	20.2	29.4	0.405
Graft complications at 180 days	1 (5.6)	0 (0)	—
Length of stay (days)	2.8	3.5	0.306

The values are expressed in n (%).

healing is a promising but not well-explored option. Risk of complications in STSG placement vary based on patient demographics, comorbidities, and recipient graft site.[21] However, recent reports exploiting FG's adherent properties for skin graft fixation are increasing, especially in animal research[22–26] and clinically in burn patients.[27–29] These clinical studies, although small in quantity, have reported positive outcomes with fewer graft loss and a decrease in hospital stay.[27–29]

Although current literature regarding the use of FG is becoming more frequent, studies evaluating STSG fixation are thwarted by unmatched patient populations, with limited clinical outcomes, minimal follow-up, and lack a cost analysis. Only 2 studies in the literature have compared FG versus traditional approaches for STSG fixation in a general reconstructive, nonburn wound patient population. Reddy et al[30] examined a prospective cohort of patients and compared surgical outcomes at 14 days of follow-up between groups whose STSGs were fixated using FG versus skin staples or suture. Despite the small cohort, lack of matched study participants, and short-term follow-up, the group anecdotally noted reduction in operating room duration, better hemostasis, and better graft fixation in the FG group. Han et al[31] developed a similar prospective study with 30-day follow-up, which found statistically significant reductions in collection formation and graft necrosis and increased graft take, with FG fixation methods. The group concluded that FG's utility in STSG fixation was superior to suture- or staple-only fixation, despite the short-term follow-up analyses and lack of cost data.

Table 6. Summary of Total Cost, Charges, and Total Direct Cost for Patients Receiving Fibrin Glue Fixation and Suture Only STSG Fixation

	Fibrin Glue (n = 10 Patients)	Suture Only (n = 10 Patients)	*P*
Charges	$120,336	$183,750	0.496
Total direct cost	$16,542	$24,266	0.545
Total no. wounds	18	10	—

The efficacy of FG for the fixation of large lower extremity wounds was expressed in this preliminary analysis based on 180 days of postoperative follow-up and detailed records regarding time to 100% graft take. There was only one instance of delayed graft healing in the FG group, which fully healed after 7 weeks of standard wound care and without any additional surgical interventions. Furthermore, comparing time to graft take between the 2 groups revealed no significant differences (20.2 and 29.4 days, $P = 0.450$), underscoring the likely similarities in the effectiveness and utility of FG.

A potentially added benefit of using FG for STSG fixation is a reduction in operative time. Average wound-adjusted operative time was more than 10 minutes less in the FG group, demonstrating a clear trend, though not statistically significant ($P = 0.0612$). Average adjusted operative time decreased from 49.4 to 34.9 minutes, which accounts for more than a 25% reduction in time for cases using FG for STSG fixation. In a larger study, we expect that statistical significance in operative times will emerge, especially in larger wounds with multiple sites and in challenging anatomical locations. The potential ability of FG to decrease operative time, coupled with no difference in clinical outcomes, solidifies its position as a valuable tool in the reconstructive surgeon's armamentarium.

One clear indirect benefit of FG for STSG fixation, in our practice, is liberation from NPWT, which has traditionally become a common adjunct for graft stability and facilitates graft incorporation. Additionally, the use of NPWT has been reported to enhance graft take and reduce the rate of reoperation, when compared with conventional dressings.[7] However, the use of FG for STSG fixation is thought to buttress stabilization, whereas the wound dressing protects the graft, thus eliminating the need for an

NPWT.[6,7] Ten of 11 wounds in the control arm of this study required postoperative wound VAC placement, whereas none of the patients' wounds in the FG cohort required a wound VAC ($P < 0.0001$). This liberation from NPWT is inherent within the practice of the senior author when using FG, and further studies are needed to delineate the true clinical impact of specific wound dressings.

The process of obtaining NPWT systems can be cumbersome. Wound VAC orders, management, and removal require expenditure of healthcare resources, especially for the administrative team and mid-level providers. Perhaps underappreciated, the multistep process required for VAC management (Fig. 2) relies on considerable resource allocation and contains numerous potential setbacks at each step, from insurance company authorization to device application and associated device issues. Thus, through the use of FG, such resource allocations are avoided entirely. However, additional studies are needed to comprehensively assess the outcomes of different postoperative dressings after the FG fixation of STSG.

Cost analysis revealed the total direct costs ($16,542 FG versus $24,266 SO; $P = 0.545$) and total charges ($120,336 FG versus $183,750 SO; $P = 0.496$) for the FG patients trended toward being less expensive compared with SO fixation. Although we recognize that this cost analysis does not provide distinct statistical differences between the groups, our study is able to highlight potential factors that provide a cost–benefit to using FG, including reduced operative time, decreased hospital stay, and the elimination of a wound VAC.

The use of FG for STSG fixation was fully adopted into the senior author's (JPF) practice on August 30, 2017, and has been used as the primary method of fixation for STSG. In this time, we have developed a standardized approach for utilizing FG for graft fixation (Figure 1). Early on, temporary staples were used to stabilize the graft and typically removed 1–2 minutes after the graft has dried. However, in the vast majority of recent cases, through proficiency of the operative technique, temporary fixation was not applied. Figure 3 displays a representative case of a patient who had large lower extremity defects secondary to bilateral fasciotomy incisions on both the medial and lateral aspects of his lower extremities. This patient received 4 large STSGs, all of which were fixated using FG. Figure 3E and F displays the patient's postoperative result at 7 weeks. Patients with large wound defects or multiple wounds, such as this patient, can especially benefit from FG for the purposes of both operative efficiency and preventing need for wound VAC. This preliminary analysis provides evidence for the utility of FG for STSG fixation with potential benefits for both the patient and the healthcare system.

However, there are various limitations to this study, inherent in the retrospective, nonrandomized, study design. Furthermore, due to the recent implementation of FG into our clinical practice, the patient population size was limited. These limitations contributed to an insufficiently powered analysis, resulting in minimal statistically signifi-

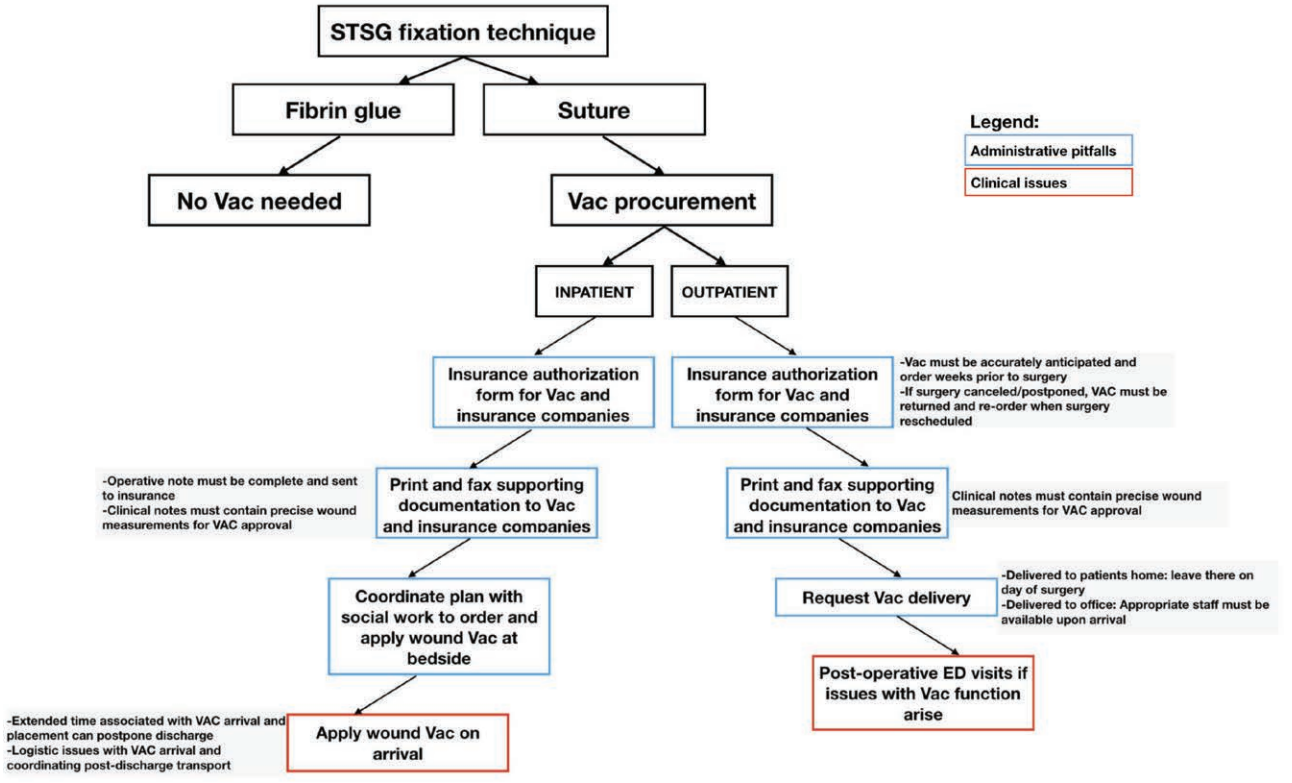

Fig. 2. Administrative and staff logistics and potential pitfalls associated with postoperative VAC procurement and use for STSG patients. Such logistical issues can be avoided in patients who receive FG for STSG fixation as they do not require wound VAC placement.

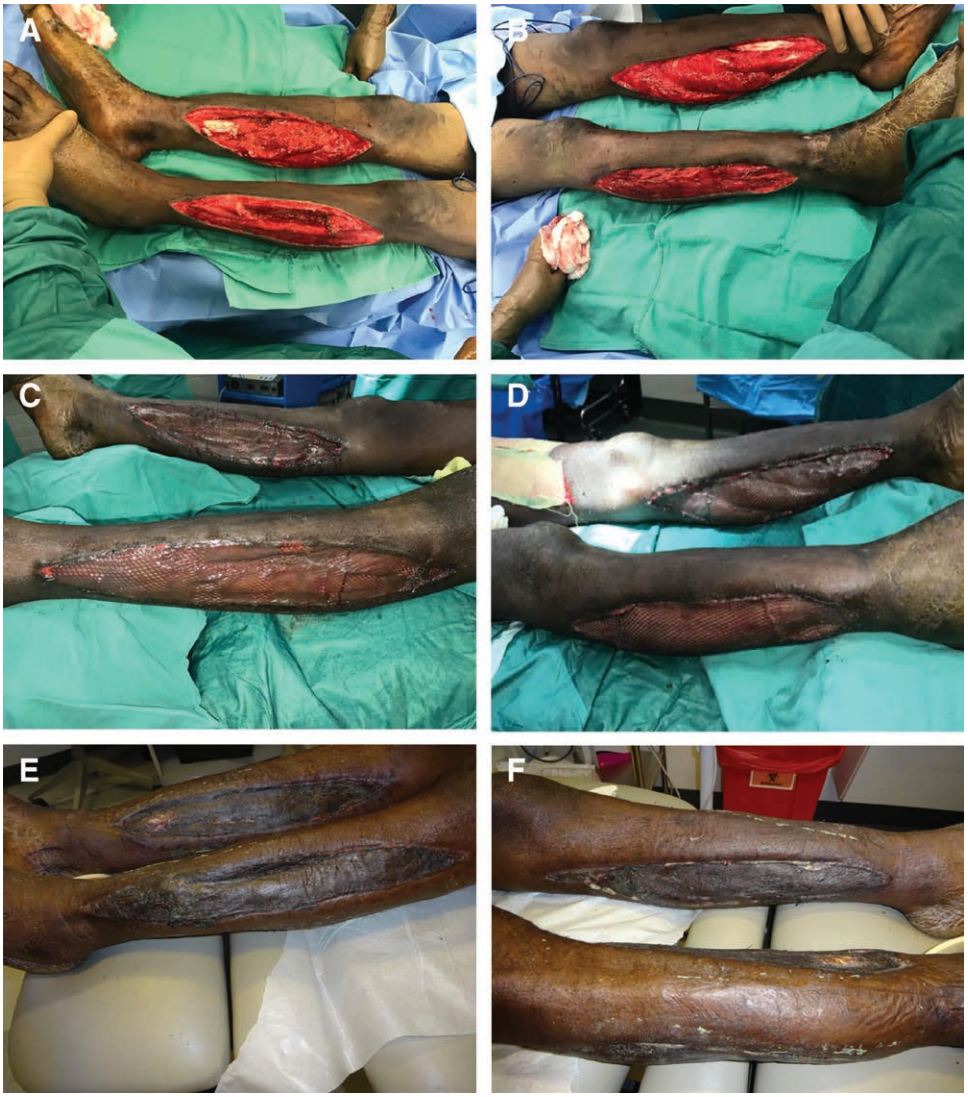

Fig. 3. Representative case example of a patient with 4 large lower extremity defects secondary to fasciotomy in need of STSG for coverage. A and B, Intraoperative photographs following debridement and wound bed preparation. C and D, Images immediately postoperatively. E and F, Images at 7 weeks of follow-up.

cant differences in outcomes. The short-term, 180-day, follow-up was an acceptable limitation, as our goal was to analyze STSG-healing rates, which can be effectively evaluated in the first 6 months postoperatively. Furthermore, although NPWT liberation is associated with FG application, the use of NPWT after the SO fixation of STSGs is standard practice for the senior author. Thus, future prospective comparison studies analyzing outcomes of FG fixation and SO fixation with different postoperative dressings, such as bolster dressings, are needed. Additionally, a lack of consistent intraoperative microbiological specimen data limits the characterization of this patient population. Detailed study examining FG's effectiveness in the presence of different infectious organisms should be evaluated to further elucidate this concept.

Overall, this study succeeded as a preliminary study in comparing matched cohorts of patients undergoing FG fixation to SO fixation for STSG adherence. The implementation of FG for STSG fixation has the potentiality to benefit practice workflow, by minimizing healthcare expenditures, liberating both patients and providers from wound VAC procurement, and providing comparable clinical outcomes to SO fixation.

CONCLUSIONS

Through this preliminary comparative study, the use of FG for STSG fixation has shown promising results when compared with traditional fixation methods, in the setting of clinical outcomes. Specifically, in our practice, a trend was identified toward reduced operative time and a diminished need for postoperative NPWT. Future research consisting of larger, prospective, randomized trials is warranted to better understand the clinical utility and cost effectiveness of FG for STSG fixation

and the impact of various postoperative wound dressings on healing.

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