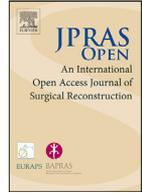Contents lists available at ScienceDirect

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Use of oxidized regenerated cellulose (ORC)/collagen/silver-ORC dressings to help manage skin graft donor site wounds

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A R T I C L E   I N F O

A B S T R A C T

Harvesting donor site explants for split-thickness skin grafting creates an iatrogenic wound that presents additional challenges to clinicians due to morbidities such as persistent bleeding, pain, infection, and delayed epithelialization. Although there have been several randomized controlled trials to compare wound dressing effectiveness, there is still a lack of standardization for donor site wound dressings.

A retrospective comparison of 59 patients that underwent split-thickness skin graft reconstructions between January 2017 and September 2018 was performed. Donor sites of Group 1 patients ($n = 29$) were treated with a transparent film dressing and transitioned to petrolatum gauze dressings if exudate management became problematic; Group 2 patients ($n = 30$) were treated with oxidized regenerated cellulose/collagen/silver-oxidized regenerated cellulose (ORC/C/Ag-ORC) dressings. Evaluations of time to epithelialization, number of dressings required, signs of inflammation, and objective pain were compared between groups.

Group 1 was comprised of 18 female and 11 male patients, whereas Group 2 was comprised of 14 females and 16 males. There were no significant differences between groups when comparing age, sex, comorbidities, or donor site size (area or depth). Patients in Group 2 had a significantly shorter time to complete re-epithelialization ($P < .0001$), fewer dressing changes ($P < .0001$),

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and less objective pain as measured by the need for opioid pain mediation ($P < .0001$) when compared to Group 1. The percentage of patients with signs of inflammation was also lower for Group 2, although this difference was not statistically significant ($P = .0797$).

Although prospective, controlled studies are still needed, data from this study suggest that ORC/C/Ag-ORC dressings could become a more effective alternative for the management of donor site wounds, especially in patients with known risk factors for wound healing.

Introduction

Split thickness skin grafts (STSGs), which were first described in medical literature in the late 1860s and likely date back to ancient India,[1,2] are now an essential method on the reconstructive ladder and a widely utilized technique for wound reconstruction.[3] One negative consequence of STSGs is that harvesting donor site explants create a secondary, iatrogenic wound that is often managed so that it heals by secondary intention. Donor site wounds create additional challenges due to morbidities (e.g., delayed epithelialization, persistent bleeding, prolonged drainage, and pain) and frequently prohibit skin grafting and expeditious coverage of the recipient wound, especially in patients with known risk factors for delayed wound healing (e.g., advanced age, obesity, poorly controlled diabetes mellitus, and vascular disease).[4] Thus, finding dressing solutions that further reduce donor site morbidities would be a great benefit to both patients and healthcare practitioners (HCPs).

Two of the most traditional dressings used on donor sites are transparent film dressings (e.g., 3M™ Tegaderm™) and sterile, petrolatum-based, fine-mesh gauze dressings (e.g., 3% bismuth tribromophenate, or Xeroform® Petrolatum gauze). Transparent film dressings and other moist wound-healing products have been reported in several meta-analyses and systematic literature reviews to provide superior outcomes for donor site wounds when compared to non-moist dressings regarding faster re-epithelialization rates and lower patient pain.[5–9] However, transparent film dressings often have significant issues with exudate management,[9] and HCPs will switch to petrolatum-based gauze dressings or start with petrolatum-based gauze even though they are non-moist dressings. In fact, Blair and Brown, in 1929, described the use of a Xeroform® dressing to help manage the first intermediate-thickness STSG donor sites,[10] and Petrolatum-based gauze dressings have been reported as standard care for donor site wounds at many facilities.[11–14]

The oxidized regenerated cellulose/collagen (ORC/C) dressing is an open-pored, freeze-dried matrix that absorbs exudate and forms a gel when placed onto the wound bed.[15] For the ORC/C/silver-ORC (ORC/C/Ag-ORC) dressing, silver-ORC fibers are added to the ORC/C liquid suspension before freeze-drying.[15] A recent prospective, non-comparative study demonstrated favorable clinical outcomes when using the ORC/C/Ag-ORC dressing to help manage intermediate-thickness STSG donor sites in patients with multiple comorbidities.[16] However, there have been no studies comparing the effects of ORC/C/Ag-ORC dressings, or ORC/C dressings, with other dressing types on clinical outcomes related to donor site wounds. In this study, a retrospective comparison of the effects of ORC/C/Ag-ORC dressings or traditional dressings (i.e., an initial transparent film dressing that was or was not transitioned to petrolatum-based gauze dressings) on skin graft donor site morbidities was performed. The data compared between groups included: demographic information, time to re-epithelialization, the number of dressings required, signs of inflammation, and objective pain based on the need for narcotic pain medications.
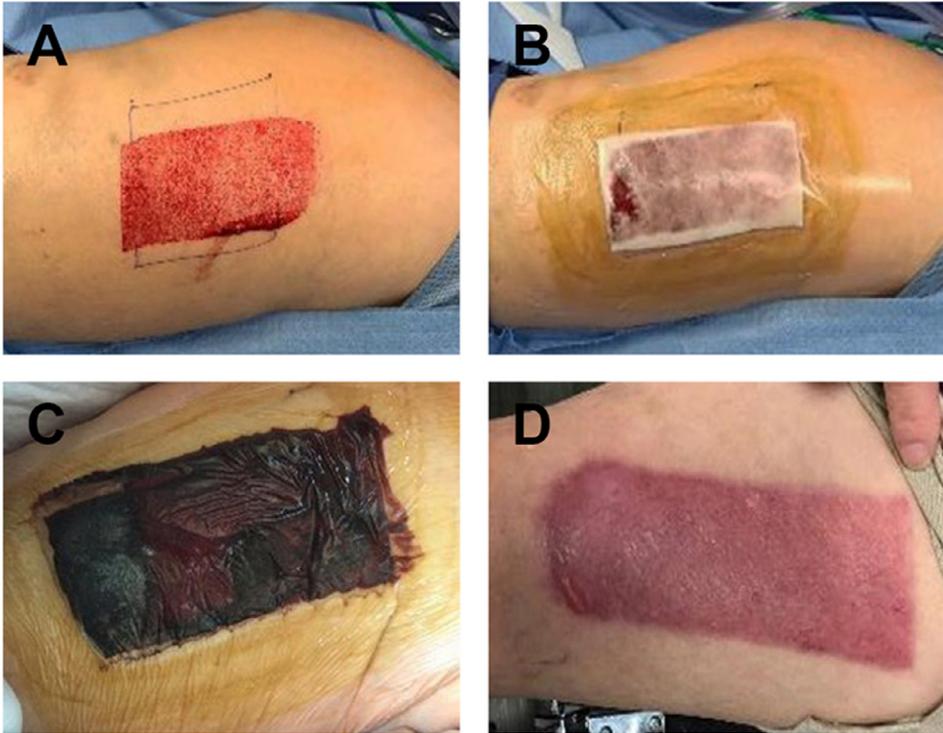
Figure 1. Representative case showing the application of ORC/C/Ag-ORC dressing. (A) A donor site wound immediately after harvesting STSG explant from the anterolateral thigh on Day 0. (B) Representative donor site wound immediately after application of the primary ORC/C/Ag-ORC dressing and the secondary layer, which was a transparent film dressing. (C) Donor site wound on Day 6 before re-applying the ORC/C/Ag-ORC dressing and changing the secondary dressing. (D) Donor site wound on Day 11 after removal of dressings.

Methods

A non-blinded, retrospective assessment of 59 consecutive patients that had most recently underwent split-thickness skin graft reconstructions by a single surgeon between January 2017 and September 2018 at a large medical center in the Chicago Metropolitan Area was performed. Demographic information was collected for each patient at the time of the STSG procedure. Surgeries for both groups of patients were performed under general anesthesia, and donor site skin on the proximal anterolateral thigh was shaved and prepared for surgical harvesting by applying antiseptic agents (e.g., 2% chlorhexidine gluconate solution with 70% isopropyl alcohol or beta iodine solution). Each patient underwent a 0.012-inch STSG procedure using an air-powered dermatome (Zimmer Biomet®, Dover, OH) to perform the donor site harvest (Figure 1(A)). While placing the STSG onto the recipient site, the donor site was temporarily covered with saline-soaked laparotomy pads.

After placing the STSG onto the recipient site, laparotomy pads were removed from the donor site. A sterile, waterproof, transparent film dressing (3M™ Tegaderm™ Dressing, St. Paul, MN) was then applied to the donor sites of patients in Group 1. Twenty four of the 29 patients in Group 1 were then transitioned within 12–18 h to a petrolatum-based gauze dressing (3% bismuth tribromophenate) due to excess exudate collecting under the film. Donor sites of patients in Group 2 (i.e., the ORC/C/Ag-ORC group) were covered with a sterile, ORC/C/Ag-ORC dressing (Promogran PRISMA™ Matrix; KCI, An Acelity Company, San Antonio, TX), which was then covered with a sterile and waterproof transparent film dressing (3M™ Tegaderm™ Dressing) as a secondary layer (Figure 1(B)). Dressings and wounds of patients in both groups were first checked on the day following surgery. Primary dressings were

Table 1
Demographics and characteristics.

Parameter	Group 1 ($n = 29$)	Group 2 ($n = 30$)	P-value
Age (years)			
Mean ± SD	51.62 (14.24)	52.10 (14.76)	0.8995[a]
Median (range)	54 (26–81)	51.5 (22–82)	
Sex, n (%)			
Female	18 (62.07%)	14 (46.67%)	0.2993[b]
Male	11 (37.93%)	16 (53.33%)	
Donor site area (cm^2)			
Mean ± SD	69.67 ± 9.45	69.13 ± 6.81	0.8019[a]
Median (range)	71 (57– 84)	68.7 (58.6–86)	
Number of comorbidities per subject			
Mean ± SD	1.48 (1.96)	1.47 (1.55)	0.9721[a]
Median (range)	1.0 (0–7)	1.5 (0–5)	
Comorbidities/medical history, n (%)			
Atrial fibrillation	3 (10.34%)	1 (3.33%)	0.3533[b]
Asthma	3 (10.34%)	2 (6.67%)	0.6707[b]
Coronary artery disease	3 (10.34%)	3 (10.0%)	>0.99[b]
Congestive heart failure	2 (6.90%)	3 (10.0%)	>0.99[b]
Chronic obstructive pulmonary disease	3 (10.34%)	3 (10.0%)	>0.99[b]
Diabetes mellitus	7 (24.14%)	5 (16.67%)	0.5321[b]
Hyperlipidemia	3 (10.34%)	5 (16.67%)	0.7065[b]
Hypertension	10 (34.48%)	11 (36.67%)	>0.99[b]
Hypothyroidism	2 (6.90%)	2 (6.67%)	>0.99[b]
Peripheral vascular disease	4 (13.79%)	4 (13.33%)	>0.99[b]
Obesity	3 (10.34%)	4 (13.33%)	>0.99[b]

[a] *P*-value is from a two-sample *t*-test for continuous data.
[b] *P*-value is from a Fisher's exact test for categorical data.

changed (Group 1) or reapplied (Group 2) according to the author's discretion when the maximum capacity of the dressings had been saturated (Figure 1(C)). Secondary dressings for patients in Group 2 were changed along with primary dressing re-applications.

Donor site wounds in both groups were allowed to completely heal by secondary intention (Figure 1(D)). Evaluations of donor site area, donor site depth, time to epithelialization, number of additional dressings required, signs of inflammation as assessed by the physician (e.g., surrounding redness, pain, swelling, and/or fever), and use of opioid pain medication (as a measure of objective pain) were compared between groups. In all cases where signs of inflammation were detected, the patients were administered oral, broad spectrum antibiotics.

Statistical analysis

All data except objective pain and signs of inflammation were measured on a continuous scale; objective pain scores and signs of inflammation were reported on a binary scale. For inflammation, a "0" indicated no signs of inflammation, whereas a "1" indicated signs of inflammation. For pain, a "0" indicated that no narcotic pain medicine was necessary, whereas a "1" indicated that narcotic pain medicine was necessary. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) software. Continuous variables were compared between groups using a *T*-test, and categorical data was compared by Fisher's exact test. Statistical significance was determined at an alpha of 0.05.

Results

During the study period, a total of 59 patients underwent split-thickness skin grafts for reconstruction procedures including traumatic wounds, skin cancer reconstruction, muscle flap coverage, and lower extremity reconstruction. There were 29 patients in the Group 1, comprised of 11 male and 18 female patients, and 30 patients in Group 2 (16 male and 14 female patients) (Table 1). Overall, the mean age of the patients in this study was 51.9 ± 14.4 years (ranging from 22–82 years). There
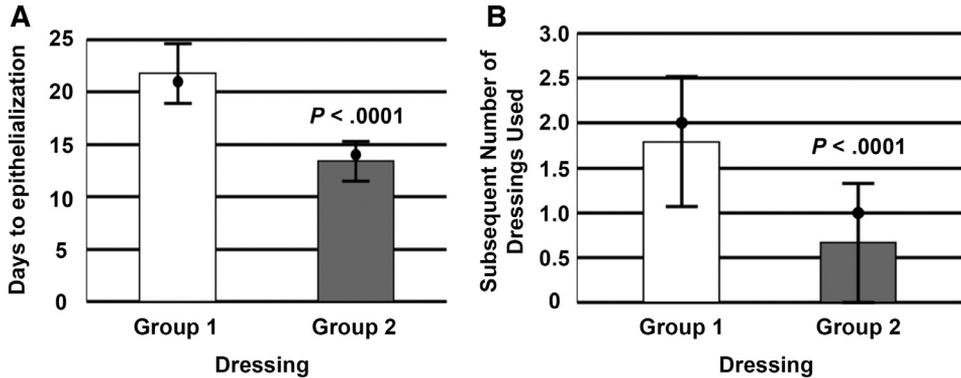
Figure 2. Effect of ORC/C/Ag-ORC dressing on time-to-epithelialization and number of subsequent dressings. (A) Bar graph indicating the mean (±SD) time until donor site re-epithelialization for Group 1 (white bar) or Group 2 (gray bar). The median time until donor site re-epithelialization is indicated by the black circle within the error bars. (B) Bar graph indicating the mean (±SD) number of subsequent dressings for Group 1 (white bar) or Group 2 (gray bar). The median number of subsequent dressings is indicated by the black circle within the error bars.

Table 2
Pain and inflammation analyses.

Parameter	Group 1 ($n=29$)	Group 2 ($n=30$)	P-value[a]
Number of subsequent dressings, n (%)			
0	0	13 (43.3%)	<0.0001
1	11 (37.9%)	14 (46.7%)	
2	13 (44.8%)	3 (10.0%)	
3	5 (17.2%)	0	
Opioid medication use, n (%)			
Yes	23 (79.3%)	4 (13.3%)	<0.0001
No	6 (20.7%)	26 (86.7%)	
Signs of inflammation, n (%)			
Yes	7 (24.1%)	2 (6.7%)	0.0797
No	22 (75.9%)	28 (93.3%)	

[a] *P*-value is from a Fisher's exact test for categorical data.

were no significant differences between the two groups when comparing patient age or patient sex (Table 1). There were also no significant differences in the number of overall comorbidities per patient or the number of specific comorbidities when comparing the groups; comorbidities included coronary artery disease, hyperlipidemia, diabetes mellitus, and hypertension (Table 1). Overall, donor sites had a mean area of 69.4 ± 8.15 cm^2, ranging from 57 cm^2 to 86 cm^2. There was no statistical difference between groups when comparing the wound areas, and each donor site had a depth of 0.012 inches ($P = .8019$; Table 1).

When comparing the two groups, there was a significantly fewer number of days until re-epithelialization in patients from Group 2 (average of 13.4 ± 1.89 days) when compared with Group 1 (average of 21.8 ± 2.87 days) ($P < .0001$; Figure 2(A)). Patients in Group 2 also had significantly fewer dressing changes (average of 0.67 ± 0.66 subsequent dressings) when compared to patients in Group 1 (average of 1.79 ± 0.73 subsequent dressings) ($P < .0001$; Figure 2(B)). Ninety percent of patients in Group 2 received 1 dressing change or fewer, and the remaining 10% had 2 dressing changes (Table 2); all patients in Group 1 had 1 or more dressing changes with 44.8% of patients having 2 subsequent dressings (Table 2).

In addition to the time to re-epithelialization and number of dressing changes, objective pain, as measured by the necessity for narcotic pain medication, was compared between groups. A significantly lower percentage of patients in Group 2 (13.3%) required narcotic pain medication when compared to Group 1 patients, where 79.3% of patients required opioid pain medications ($P < .0001$;

Table 2). Lastly, signs of inflammation were compared between groups. Although there was a lower percentage of patients in Group 2 (6.7%) with signs of inflammation when compared to Group 1 (24.1%), this difference did not achieve statistical significance (*P* = .0797; Table 2).

Discussion

STSGs, which are categorized, in part, based on the thickness of the explant, can be (i) less than 0.3 mm in depth (i.e., thin STSGs), (ii) between 0.3 mm and 0.45 mm thick (i.e., intermediate STSGs), or (iii) between 0.45 mm and 0.6 mm thick (i.e., thick STSGs).[17] In this study, all the donor site wounds resulted from intermediate-thickness explants (0.012 inches, or approximately 0.3 mm) from the proximal anterolateral thigh. ORC/C/Ag-ORC dressings covered with a semi-occlusive, transparent film dressing favorably affected the time to epithelialization for donor sites, the number of dressing changes, and narcotic pain medication use (to objectively measure pain) in patients when compared with only a semi-occlusive, transparent film dressing that was transitioned to petrolatum-based gauze in most cases. These data could potentially be extrapolated to thin STSGs since a previous study showed that healing rates for donor site wounds were not correlated with depth for wounds ranging from 0.12 mm to 0.42 mm.[14]

Previous studies using the same dressings as those in Group 1 of this study have reported times to re-epithelialization ranging from 9.47 days to 12.4 days,[12–14] whereas Group 1 in our study required a mean time of 21.8 ± 2.9 days for re-epithelialization (Figure 2(A)). This discrepancy can be explained, in large part, by differences in comorbidities between the studies. Patient populations in previous studies were younger in comparison to this study (ranging from 33 to 36.5 years) with less comorbid medical conditions that impaired wound healing.[12–14] In contrast, both groups in our study contained a number of comorbidities known to impact wound healing (e.g., advanced age, hypertension, and diabetes mellitus). Instead, the time to re-epithelialization in Group 1 of this study is similar to that reported in a randomized trial using a different brand of petrolatum-based gauze, whereby older patients (mean age of 62 years) with comorbid conditions required a mean of 27.9 days for re-epithilializaiton.[18] Furthermore, the time to re-epithelialization in our ORC/C/Ag-ORC group is similar to a previous study, which reported that older patients (mean age of 71.6 years) with multiple comorbidities that underwent complete wound re-epithelialization in an average of 17.2 days when using ORC/C/Ag-ORC dressings.[16] The variations in time to re-epithelialization between studies could also possibly be explained, in part, by differential definitions of epithelialization. In this study, a strict definition of complete epithelialization was used, in which complete healing was defined as having no remaining scab on the wound.

Another important finding from this study was that a lower percentage of patients in Group 2 (the ORC/C/Ag-ORC group) required opioid pain medication use, used as an objective pain measurement, compared to Group 1. To our knowledge, this is the first comparative study of different donor site dressings that assessed pain in this manner. Previous studies that have analyzed pain related to donor site wounds have relied on patient-reported pain using scales (i.e., visual analog scale or numeric pain rating scale) or patient questionnaires.[6] Donor site dressings are one of five current modalities used to effect pain resulting from donor site wounds; the other four modalities for alleviating donor site pain include continuous subcutaneous local anesthetic (CSLA), subcutaneous anesthetic injections, topical agents, and non-pharmacological intervention (e.g., ice application).[19] Our data suggest that ORC/C/Ag-ORC dressings could be added to the list of donor site dressings that potentially help alleviate pain, and it would be interesting to know whether ORC/C/Ag-ORC dressings can be used to decrease the need for other pain management modalities (e.g., CSLAs, over-the-counter pain medications, or topical agents).

The silver that is added to the ORC/C/Ag-ORC dressing is known to have antimicrobial activity,[20] and *in vitro* studies have demonstrated that ORC/C/Ag-ORC dressings block the growth of vegetative bacterial cultures.[21] Although the ORC/C/Ag-ORC group had a fewer percentage of patients with signs of inflammation (i.e., signs or symptoms for infection) in comparison to Group 1 in this study, this difference did not achieve statistical significance. These data suggest that this study was slightly underpowered concerning this clinical outcome; however, the results could also be explained if the Group 1 dressings impacted bacterial colonization in the wound. Two previous clinical studies of donor site

wounds treated with the same petrolatum-based gauze dressing that was used in this study showed no infections[11,12]; however, an *in vitro* study showed that the gauze dressing itself did not demonstrate antimicrobial properties for 15 different bacterial species.[22] The impact of the Group 1 dressings on bacterial colonization was not quantified as part of this study.

In summary, this is the first comparative study of an ORC/C/Ag-ORC dressing for donor site wounds. Although this study was limited by a relatively small sample size and as a retrospective study with the potential for selection bias and other disadvantages of this study type, data from this study suggest that prospective, controlled studies to assess the effectiveness of ORC/C/Ag-ORC dressings in STSGs of different thicknesses and different anatomical locations (i.e., anteromedial thigh or buttocks) are warranted. If data from future studies continue to support the data provided in this study, then the ORC/C/Ag-ORC dressing could become a more effective alternative for the management of donor site wounds, especially in patients with known risk factors for wound healing. Further elucidation of effective donor site dressings could alter wound reconstruction options in multi-morbid patients where skin grafting is precluded by the donor site wound morbidities.

Conclusions

- Split thickness skin grafting is a simple and effective means of reconstructing wounds; however, donor site morbidity frequently precludes skin grafting and expeditious wound closure.
- We demonstrate via a retrospective assessment of 59 patients that underwent split-thickness skin graft reconstructions that utilization of an ORC/C/Ag-ORC dressing on donor site wounds resulted in a reduction in time to epithelialization by an average of 8 days, fewer dressing changes, and a reduction in use of opioid pain medications compared to transparent film dressings, most of which were transitioned to a petrolatum-based gauze dressing.

Declaration of Competing Interest

Dr. Chowdhry is a paid consultant for KCI, an Acelity company, and he was compensated for his time spent preparing the manuscript.

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