Even Better Than the Real Thing? Xenografting in Pediatric Patients with Scald Injury

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KEYWORDS

• Scald injury • Pediatric burn • Xenograft • Infections

KEY POINTS

- Xenografting seems a reasonable option for patients with partial-thickness scald injuries.
- Although nonoperative management may be appropriate for small/superficial burns, and autografting may be required for large/deep burns, xenografting provides rapid wound closure.
- Xenografting also permits earlier hospital discharge, reduces need for reconstruction, and should strongly be considered as first-line therapy for intermediate-depth pediatric scald injuries.

INTRODUCTION

Scald injuries remain the most common type of burn in children. More than 250,000 children are burned each year in the United States, and 100,000 of these are scald burns.[1] These numbers reflect only children burned badly enough to need medical attention and do not include children whose caretakers do not seek help. The use of xenografting in burns was described as early as 1880,[2] followed by the report of split-thickness or intermediate-thickness skin grafts in 1929.[3] Best practices on treatment of these injuries continue to evolve as new therapies become available and as understanding of immune-mediated rejection of allografts and xenografts continues to improve.

In 2004, the authors developed a new approach to these scald burns, at their institution, based on the need to standardize a pathway for wound care. Patients with partial-thickness wounds were considered for early excision and xenografting to assist with wound closure, previously a far less common procedure done in their pediatric scald population. Xenografting has previously been shown to reduce pain, have some antibacterial action as a function of its adherence, protect against physical trauma, and provide appropriate head and moisture retention.[4]

Over the following years, the authors observed an anecdotal decrease in hospital stay and improved short-term outcomes; however, there continued to be a paucity of evidence in the literature to support these results. It was also evident

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that early operative intervention for wound closure with xenografting provided the opportunity for earlier discharge to home. Decreasing hospital stay has recently been shown to directly decrease costs, reduce incidence of health care–associated infections (HAIs), and provide earlier return to activities.[5,6] The authors, therefore, hypothesized that this institutionally novel therapeutic sequence might may provide similar results in a study population.

During this time, the authors also instituted a laser practice to treat hypertrophic scars that developed from burn injuries. Although the degree of scar formation is most likely related to the depth of injury, the authors also speculated that the type of closure—xenograft, autograft, or local wound care—might also influence the development of hypertrophic scar and the subsequent need for reconstruction. With a significant amount of psychosocial development occurring during childhood and adolescence, the authors wanted to determine which of the interventions would provide the best long-term outcomes, in the shortest time frame, with the fewest interventions, to restore form and function. Children are unique compared with their adult counterparts, in that they continue to grow, and even small, initially asymptomatic scars can become problematic by not lengthening while the surrounding tissue grows.

Despite the short-term success of biologic dressings, like xenografts and allografts, in the treatment of burn wounds,[7–10] there is a paucity of information regarding long-term follow-up of children with scald injury who receive this type of wound coverage. Furthermore, long-term outcomes related to need for reconstruction, with either lasers to treat hypertrophic scars or more invasive procedures to release contracture, are not well defined. In this article, the authors report a 10-year experience with pediatric scald burns, comparing 3 different techniques of wound closure: nonoperative management, xenografting, and autografting. In addition to reporting length of stay (LOS), complications, and costs of the initial admission, reconstructive outcomes are evaluated.

METHODS

After obtaining institutional review board approval, the authors queried the institutional American Burn Association database to identify all patients under the age of 18 years who were admitted with a scald injury to the North Carolina Jaycee Burn Center. The authors identified 1867 subjects who met the inclusion criteria. The timeframe for review was a 10-year period beginning in January 2004 and extending to December 2013. These patients were then stratified into 3 cohorts based on the wound closure method: (1) nonoperative treatment with local wound care only (although this included patients who had débridement under sedation), (2) operative débridement and xenografting of the scald injury, and (3) excisional preparation and autografting of the scald injury. Patients who underwent autografting at the primary site but also had xenografting of the donor site were assigned to the autografting category.

The data points from the American Burn Association national repository database are prospectively collected, and the initial set of variables included the following: medical record number, name, age, race, gender, county of residence, admission date, injury date, percentage total body surface area (%TBSA), *International Classification of Diseases, Ninth Revision* codes for that visit, number of operating room (OR) procedures during admission, admit status (floor, step-down, or ICU), ICU days, discharge date, LOS, hospital charges, and disposition at discharge.

After initial data receipt from the burn registrar, the authors proceed with review of individual charts, securely housed in an Epic electronic health record (Epic Systems, Verona, Wisconsin), to determine information on posthospital care, which included the following data points: length of outpatient follow-up, time to outpatient referral to a plastic surgeon, OR visits as an outpatient, time to first outpatient OR procedure, number of laser treatments, time to first laser treatment, number of outpatient skin grafts, number of outpatient tissue rearrangements (adjacent tissue rearrangement [ATRs]), and the number of outpatient nerve releases.

After obtaining these additional data points, the authors then investigated the total number of HAIs, by merging the list of patients with the institutional repository of HAIs, recorded in this same timeframe, by hospital epidemiology and infection control. This allowed comparing incidence and type of infections for the 3 different groups: autograft, xenograft, and nonoperative.

Categorical variables, such as gender, plastic surgeon referral, outpatient surgery, outpatient laser, outpatient skin grafts, and tissue rearrangements, were analyzed using 2×2 and 2×3 χ^2-square tables. Continuous/nominal variables, such as age, %TBSA, ICU days, LOS, hospital charges, length of follow-up, time to plastic surgeon consult, time to outpatient OR, time to first laser, and the number of laser treatments, were analyzed using a 2-tailed *t* test. Statistical significance was assigned for *P* values less than .05.

RESULTS

Patient demographics and in-hospital variables are shown in **Table 1**. The average age of patients in the autograft group was significantly older compared with the xenograft group (5.75 vs 3.41 years old; $P<.001$). There was no difference, however, in terms of gender ($P = .38$). %TBSA of the scald injury trended larger for the autograft group compared with the xenograft group (12.6% vs 8.1% TBSA; $P = .065$). LOS, however, was significantly longer for the autograft group compared with the xenograft group (22.9 vs 5.2 days; $P<.001$). Consistent with this finding, the autograft group also had a longer stay in the ICU (7.28 vs 1.14 days; $P<.001$) compared with the xenograft cohort. Furthermore, incidence of HAIs was significantly increased for patients who required autograft (7.0% vs 0.8%; $P<.001$) compared with the xenograft cohort. Regarding the need for operative intervention, the autograft group also required statistically more visits to the OR compared with the xenograft group (1.3 vs 1.0; $P<.001$); although this is not clinically significant, this finding does reflect the need for staged excision and grafting in some of the autografted patients. The nonoperative group did require operative intervention infrequently, with an average 0.07 trips/patient, or 1 of every 14 patients, for placement of feeding tubes, superficial débridement, and dressing change under sedation.

Incidence and type of HAIs were consistent with previously published data for hospital acquired infections in burn patients,[11] with pulmonary infections the most frequently encountered (**Table 2**). The autograft group had a total of 21 infections, 7 of which were pulmonary related. In descending order of frequency, the remaining HAIs were found: catheter-associated urinary tract infection (CAUTI) (6); burn cellulitis (3); and 1 each of primary blood stream infection (BSI), secondary BSI, gastroenteritis, superficial incisional infection, and urinary tract infection (UTI). The xenograft group had 4 HAIs: pulmonary (2) and 1 each for primary BSI and superficial incisional. The nonoperative group had 18 HAIs with burn cellulitis the most frequent (8), followed by pulmonary infections (2), and 1 each of the following: CAUTI, primary BSI, gastroenteritis, UTI, cholecystitis, otitis media, superficial incisional, and meningitis.

Facility charges for the initial hospitalization were significantly greater for the autograft group compared with both the xenograft and nonoperative cohorts ($83,095 vs $25,504 and $17,571, respectively; $P<.001$) (**Table 3**). Length of follow-up was significantly longer in the autograft group compared with the xenograft group (286 days vs 104 days; $P<.001$); need for reconstructive surgery was significantly higher in this cohort as well (9.7% vs 3.5%; $P<.001$). The development of hypertrophic scarring was significantly higher in the autograft group compared with the xenograft and nonoperative groups (23.7% vs 8.5% vs 2.8%, respectively; all P values $<.001$).

Patients who required outpatient reconstructive surgery for hypertrophic scars, unstable wounds, and contractures were categorized into 3 groups: (1) contracture release and skin grafting, (2) ATR, and (3) laser therapy (pulsed dye laser photothermolysis and fractional CO_2 ablative resurfacing). Ten patients from the autograft cohort (2.9%) required additional outpatient skin grafting compared with 1 patient in the xenograft group (0.002%; $P<.0001$); 15 patients in the autograft cohort (4.4%) required outpatient tissue rearrangement compared with 9 patients in the xenograft group (1.7%; $P<.01$). There was no significant difference in terms of the number of

Table 1
Demographics and in-hospital variables

	Average Age	Male Gender (%)	Total Body Surface Area (%)	Average No. of Operating Room Visits	Length of Stay (d)	ICU LOS (d)	Incidence of Health Care–Associated Infections
Xenograft n = 534	3.41	55.4	8.08	1.0	5.24	1.14	0.8%
Autograft n = 339	5.75	58.4	12.56	1.3	22.86	7.28	7.0%
P	<.001	.38	.065	<.001	<.001	<.001	<.001
Nonoperative n = 994	4.15	54.7	5.75	0.07	5.09	0.72	1.8%
Total n = 1867	4.34	55.6	8.10	N/A	9.6	2.49	2.3%

Table 2
Health care–associated infections

	Autograft	Xenograft	Nonoperative	Total
Pulmonary	7	2	2	11
Burn cellulitis	3		8	11
CAUTI	6		1	7
Primary BSI	1	1	1	3
Superficial incisional	1	1	1	3
Gastroenteritis	1	—	1	2
UTI	1	—	1	2
Secondary BSI	1	—	—	1
Cholecystitis	—	—	1	1
Otitis media	—	—	1	1
Meningitis	—	—	1	1
Total	21	4	18	—

patients requiring outpatient laser therapy (18 patients in both the autograft and xenograft groups; $P = .16$), and the average number of laser treatments in each group was similar (3.3 average treatments for autograft and 3.7 for xenograft; $P = .2$). Only 1 nerve release was performed in each of the xenograft and autograft groups, with no patients from the nonoperative cohort requiring nerve decompression.

DISCUSSION

In summary, xenografting provides an attractive option for wound closure in partial-thickness scald burns, in the pediatric population. Carefully selected patients benefit from decreased ICU LOS, decreased length of hospitalization, and reduced charges. Furthermore, patients who undergo xenografting seem to have less incidence of hypertophic scarring and less need for reconstructive surgery. Children with deep burns and large surface areas require autografting, and patients with small superficial scald burns can be managed nonoperatively with topical antimicrobial therapy, but there is clearly a cohort of severity in between these groups, who are ideal for debridement and xenografting.

Determining the true cost of management is notoriously difficult, due to opaque cost accounting as well as adjusting for size and depth of the burn wound. Although the autograft group yielded higher inpatient charges, it also had increased LOS, ICU days, and HAIs, all of which have been shown to increase the cost of an admission.[4,5] Were the authors able to decrease these variables independently of the type of wound coverage a patient had, a proportional decrease in cost would have been likely. With xenografting, however, the

Table 3
Cost and postdischarge variables

	In-Hospital Charges	Length of Follow-up (d)	Incidence of Hypertrophic Scar[a]	Need for Reconstructive Surgery
Xenograft n = 534	$25,504	104	8.5%	3.5%
Autograft n = 339	$83,095	286	23.7%	9.7%
P	<.001	<.001	<.001	<.001
Nonoperative n = 994	$17,571	74	2.8%	1.9%
Total n = 1867	$36,450	123	7.2%	3.6%

[a] Outpatient referral to plastic surgeon used as proxy (see discussion).

authors were able to effect reduced hospital charges indirectly, by decreased overall LOS. The authors' conclusion is that rapid wound closure permits earlier discharge, through reduction of post-débridement pain. Furthermore, a shorter LOS exposed patients to fewer hospital pathogens, theoretically reducing incidence of HAIs.

The autograft group had significantly increased ICU and hospital LOSs, without having an increased %TBSA, compared with the xenograft cohort. What then accounts for these differences? First, there may be selection bias, where patients who may have suffered nonaccidental scalds would be more likely to receive an autograft, because early discharge home was not an option. The authors also considered that over the past few decades, child protection services have become more robust, and, when abuse or neglect is suspected or has to be ruled out, these patients remain hospitalized longer than for accidental etiologies. This might influence clinicians to take longer before performing surgery to see where wounds demarcate, instead of trying to obtain wound coverage as early as possible for discharge home. Individual chart review from the authors' electronic health records did not provide accurate information regarding the incidence of nonaccidental scalding across the 3 treatment groups.

The pattern of autografted patients requiring more resources continued into the outpatient arena. Referral to plastic surgeon as an outpatient was used as a proxy for development of hypertrophic scarring. The authors found by individual chart review that these patients were seen by the senior author (C.S. Hultman) almost exclusively for this reason and, therefore, determined that referral would serve as an accurate proxy of this variable. The etiology and exact mechanisms for hypertrophic scarring remain elusive. Why the xenograft group had a lower incidence of hypertrophic scarring, compared with the autograft group, remains unknown, but may be due to the increased depth of injury requiring replacement of damaged dermis. In 2006, Feng and colleagues[12] compared xenografting to the exposure method, citing an experience of 535 patients over 8 years and presenting 20 individual cases. Their treatment group with xenografting had significantly decreased scar hyperplasia and improved outcomes compared with nonoperative management. The authors theorized that a single dressing would have less damage to the dermis than multiple dressing changes and that a xenograft provided the wound bed the extracellular support needed for rapid healing. This was a clinical study only and did not include histopathologic specimens or measurements of tissue growth factors to compare the 2 groups.

The histopathologic issue was partially addressed using a rat model in 2013 by Chen and colleagues.[13] This study compared xenografting to a povidone iodine cream to determine which group had better growth factors and collagen deposition. They found that the xenograft group had increased collagen, proliferating cell nuclear antigen, K10, β1 integrin, platelet-derived growth factor, epidermal growth factor, and fibroblast growth factor. The investigators hypothesized that these factors provided the xenograft group better collagen synthesis, stem cell proliferation/differentiation, and ultimately improved burn wound healing. Unfortunately, without a direct comparison to an autograft group, it is difficult to say if xenografting would have a similar expression of these cytokines as autografting.

In 2013, Hermans[9] reported their modified systematic review to determine if there was a clinical difference between xenografting and allografting. He concluded that either type of skin substitute seemed to promote rapid wound healing and re-epithelialization.[9] Barone and colleagues,[14] in 2014, evaluated xenografts vs allografts using a miniature swine knockout model where the α-1,3-galactosyltransferase enzyme was removed to prevent hyperacute rejection, due to preformed antibodies to the α-1,3-galactose carbohydrate moiety on porcine cells. They found that the knockout dermis and allograft dermis both survived 11 days without signs of hyperacute rejection. Given the ability of allografts and xenografts to permit wound closure and potentially become incorporated, at least at the level of the dermis, these biomaterials are poised to play an increasing role in resurfacing of burn wounds. Even simple modifications to xenografts, such as the manufacturing of nonmeshed grafts for use on the face to avoid imprinting, can have significant long-term cosmetic benefit.[15,16]

Close attention to the overall cosmetic outcomes by modifying operative technique continues to be of interest. In 2011 Duteille and Perrot[17] published their findings that using a Versajet for débridement in combination with xenografting in 20 patients. They claimed better cosmetic results in facial burn reconstruction, stating that the Versajet (Smith & Nephew, PLC; London, UK) was particularly adapted to facial contours compared with traditional dermatomes and Weck blades (Cadence, Staunton, VA), used for tangential excision.[17]

Finally, although the authors compared xenografting to autografting, several recent publications have proposed combining the 2 methodologies. In

2011 Sun and colleagues[18] used microskin autografts under a layer of split-thickness xenografts for large surface burn coverage with good result in 31 patients with deep burn wounds. In 2013 Chen and colleagues[19] applied small portions of xenografts in their autografted wounds to test if having a combination therapy changed the wound healing process and the final results in 30 patients. They found these cografted areas tended to have healed well with no scar contracture and demonstrated a continuous basal membrane, a mature stratum corneum, rete peg formation, a uniform dermal collagen fiber structure, and fewer capillaries. They also demonstrated improved shape, and functional recovery compared with pure split-thickness autografts.

The obvious limitation of this article is that patients were not randomized into the 3 treatment groups of (1) nonoperative management, (2) débridement and xenografting, and (3) excision and autografting. Surgeons chose 1 of these 3 groups, presumably based on wound characteristics, clinical judgment of time to healing, family resources, and potentially suspicion of child abuse or neglect—which would necessarily mandate a longer LOS. Nevertheless, the data are convincing that xenografting for pediatric patients with scald injury—usually a partial-thickness burn capable of re-epithelialization—is appropriate and safe for large portion of this population. A prospective, randomized trial would help solve the additional questions that remain.

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