Surgical management and hypermetabolic modulation of pediatric burns
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COST-EFFICACY OF CULTURED EPIDERMAL AUTOGRRAFTS IN MASSIVE PEDIATRIC BURNS

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ABSTRACT

Objective
To assess the efficacy of cultured epidermal autografts (CEA) for closure of burn wounds in pediatric burn patients with full thickness burns of more than 90% total body surface area.

Summary Background Data
Paucity of donor sites in massive burns makes the use of expanded skin of paramount importance. CEA techniques have been used in burned patients with differing and controversial results. The true impact and efficacy of such techniques in massive burns remains uncertain.

Methods
Patients with full-thickness burns of more than 90% body surface area treated between May 1988 and May 1998 were studied. Patients grafted with CEA were compared with patients grafted with conventional meshed autografts. Rates of death and complications, length of hospital stay (LOS), hospital cost, acute readmissions for reconstruction, and quality of scars were studied as outcome measures.

Results
Patients treated with CEA had a better quality of burn scars but incurred in a longer LOS and higher hospital cost. Both groups had comparable readmissions for open wounds, but patients treated with CEA required more reconstructive procedures during the first 2 years after the injury. The incidence of sepsis and pneumonia in both groups was comparable.

Conclusions
Conventional meshed autografts are superior to CEA for containing hospital cost, diminishing LOS, and decreasing the number of readmissions for reconstruction of contractures. However, the use of CEA provide better quality of scars such that perhaps future research should focus on bioengineered dermal templates that promote take and diminish long-term fragility.
INTRODUCTION

Severe full thickness burns covering more than 90% of the total body surface area (TBSA) continue to pose an immense challenge to even the most experienced burn teams. In the past few decades, the burn-related death rate has declined dramatically, and this can be attributed in part to early excision and closure of the burn wound. Currently, even children sustaining full-thickness burns of more than 90% TBSA have a better than 50% rate of survival1.

The approach to skin coverage in the massively burned patient depends on the type and extent of the injury. Burns of less than 30% TBSA can be covered with autograft skin at one operation. In full-thickness burns of more than 30% TBSA, however, the autograft donor site is quickly exhausted, so that alternative skin coverage is necessary. This is particularly true in patients with massive burns, in whom a paucity of donor sites makes skin substitutes and the use of expanded skin of paramount importance. For years, these patients have been treated with traditional methods of widely expanded meshed autografts with an overlay of cadaveric allograft2,3. More recently, the use of culture epidermal autografts (CEA) has been advocated for wound closure in massive burn injury4. Nevertheless, cost, long-term fragility, and the lack of an optimal dermal equivalent for CEA have restricted its routine use 5,6. Recurrent open wounds, increased rates of burn scar contractures, and troublesome rehabilitation are also arguments precluding CEA use. The use and the efficacy of CEA in full-thickness burns of more than 90% TBSA, therefore, are still uncertain. We studied our patient population with full thickness burns of more than 90% TBSA to determine factors affecting survival and the outcomes in patients treated with CEA.

MATERIALS AND METHODS

Study population

All pediatric patients with full-thickness burns more than 90% TBSA treated at the Shriners Burns Hospital in Galveston, Texas between January 1988 and January 1998 were examined. Patients who were treated with CEA were identified and compared with a control cohort of patients not treated with CEA. Only patients surviving more than 3 weeks (time for CEA grafting) were analyzed for measures comparing CEA versus no CEA.

Surgical technique

All patients were resuscitated according to the Galveston formula (5000 mL Ringers lactate/m² body surface area burned + 2000 mL Ringers lactate/m² body surface area) given in continuous increments over the first 24 hours. Within 24 hours of admission, patients underwent wound excision of all full-thickness burns and were covered with autografts from available donor sites and cadaver allografts. Based on the attending surgeon’s choice, during the first operation a full thickness skin biopsy
was harvested for CEA culture (Genzyme, Cambridge, MA). Patients returned at weekly intervals to the operating room for further autografting and replacement of allografts. After approximately 3 weeks, CEA grafts were ready for transplantation. Take of CEA was assessed at 1 week after the application by the attending surgeon. Patients who received CEA were returned to the operating room only for further autografting to areas of graft loss or epidermolysis. Autografts were initially meshed 4:1 and applied to large surfaces. As the patient’s recovery progressed and the area open diminished, 2:1 meshing patterns and sheet grafts were used.

During the entire hospitalization stay, all patients received nutritional supplementation through a nasoduodenal feeding tube with Vivonex TEN (Sandoz Nutrition, Minneapolis, MN), an elemental formula containing 82.3% carbohydrate, 3% fat (linoleic acid), and 14.7% protein. Caloric intake was given at a rate to deliver 1500 kcal/m² body surface burned + 1500 kcal/m² body surface area. Rehabilitation was started on admission in a passive and active program.

**Study design**

Patients treated with CEA were compared to patients treated with conventional autografting techniques to assess the efficacy of CEA. Data collected included the total number of operations, area grafted with CEA, CEA “take”, CEA grafts lost and subsequently autografted, complications, length of hospital stay (LOS), overall hospital cost, reconstructive operations during the first 2 years, and quality of scars.

Surface areas were calculated by plotting the height and the weight of the patients in a standard nomogram. The areas grafted with CEA, areas lost, and areas autografted were calculated by measuring the total amount of CEA (cm²), and autograft size applied at surgery. Donor site healing was assessed by the number of days required for removal of a standard donor-site dressing. Hospital costs were estimated for individual patients by multiplying hospital days by $2,000 and adding the costs of CEA. Sepsis was defined as pathologic bacteremia on blood culture, and pneumonia was defined as lung infiltrate on chest x-ray combined with fever and a pathologic organism isolated on a class III sputum.

Burn scars were assessed 2 years after the injury by three separate investigators. Each observer analyzed all patients, and all three sets of observations were compared with the rest of the observers’ rating scores. Time from injury to reconstruction and number of reconstructions performed for burn scar contractures and cosmesis in the first 2 years after injury were quantified.

Scars were assessed for surface, border height, thickness and color difference. The burn scar rating scale introduced by Yeong et al was used to determine the degree and quality of scars. These scars were assigned a score in each of the former categories. Scores could range from –1 to 4. A score of 0 in any of the former was considered normal, or a quality matching the adjacent normal skin. A score of –1 meant atrophy, depression of borders, or hypopigmentation. Scores from 1 to 4 signified increasing degrees of severity of hypertrophy, sharp borders and hyperpigmentation. To compare the different scar rating results in the two groups over time,
Rank values were assigned to all observations in columns from smallest to largest. Equal values were tied in rank, and an averaged rank was assigned to all tied values. This rank was the average of the ranks that would have been assigned to all the tied values if they were not tied. The rank transform assigned integer values for data analysis.

Data are shown as mean ± standard error for parametric data and median and range for nonparametric data. Statistical analysis was performed with an unpaired t-test and the Mann-Whitney rank sum test, the Fisher exact test, and the Kappa test for interrater agreement. Significance was accepted at p < 0.05.

RESULTS

Patient Population

During the 10 years from May 1998 to May 1998, 32 pediatric patients with full-thickness burns of more than 90% TBSA were treated at the Shriners Burn Hospital in Galveston, Texas. Twelve patients died before day 21 (estimated day of CEA grafting), and only one patient died after day 21. The raw death rate of this severely burned cohort of patients was 40%; conversely, the survival rate was approximately 60% (Fig. 1).

Figure 1
Kaplan-Meier survival graph for children with more than 90% total body surface area burns
The mean age of all patients admitted during the study period (survivors and nonsurvivors) was 8.2 ± 1.9 years, with the percentage TBSA burned of 94.1% ± 2 and a percentage of full-thickness burns of 92.5% ± 1.5. All patients had inhalation injury, which was diagnosed by bronchoscopic examination on admission.

Patient demographics for CEA and non-CEA (traditional grafting techniques) groups are shown in Table 1. Patient groups were comparable. When the initial injury characteristics were compared to those patients that died before day 21, there were no differences in terms of delay in resuscitation or burn shock. Patients who died, however, presented a 70% incidence of anoxic brain injury and 20% incidence of brain death. These brain injuries were significantly higher in nonsurvivors compared with patients who survived (p<0.001).

Comparison of CEA and non-CEA groups

Twenty patients survived to day 21. Eight patients were treated with CEA and 12 with traditional (non-CEA) techniques. All patients in the CEA group survived, whereas one patient in the non-CEA group died on day 35 of pulmonary thromboembolism (100% survival vs. 91%, p=0.796). Before day 30, patients in the CEA and non-CEA groups underwent similar number of operations (5.2 ± 0.7 vs. 4.1 ± 0.5), but the number of operations after day 30 in the acute hospital stay was significantly higher in the CEA group (7.1 ± 1.1 vs. 3.6 ± 0.6; p=0.03, Table 2). Donor-site healing times for all operations in the acute hospital stay were similar in both groups (7 ± 0.1 days in CEA vs. 6.6 ± 0.2 days in non-CEA), and the incidence of sepsis and pneumonia in both groups was comparable (three cases of pneumonia and two of sepsis in the CEA group and two cases of pneumonia and two of sepsis in the non-CEA group; p>0.05). Patients treated with CEA had a significantly longer hospital LOS (p=0.03), and the addition of the increased LOS and the cost of CEA produced

<table>
<thead>
<tr>
<th></th>
<th>CEA group (n=8)</th>
<th>Non-CEA group (n=12)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>10.5 ± 2</td>
<td>6.1 ± 1.3</td>
</tr>
<tr>
<td>TBSA-full thickness (%)</td>
<td>92.5 ± 1.9</td>
<td>91.2 ± 1.2</td>
</tr>
<tr>
<td>Inhalation injury (%)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

CEA, cultured epidermal autografts; TBSA, total body surface area
Data presented as mean ± SEM

Table 1
Patient Demographics
a significantly greater hospital cost for the children treated with CEA (see Table 2). Three patients (37.5%) in the CEA group and four patients (33.3%) in the non-CEA group received recombinant human growth hormone. The dosage was 0.2 mg/kg/day in both groups. Subgroup analysis among patients treated with or without the hormone showed no significant differences. Donor-site healing times and LOS are shown in Table 3.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison of Groups</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CEA group (n=8)</td>
</tr>
<tr>
<td>Total number of operations</td>
<td>13 ± 1.3</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>128 ± 14.3</td>
</tr>
<tr>
<td>Cost per patient (x1000USD)</td>
<td>304 ± 31</td>
</tr>
</tbody>
</table>

CEA, cultured epidermal autografts
Data presented as mean ± SEM
(* p<0.05, Non-CEA vs. CEA, unpaired t—test)

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Donor-Site Healing Time and Length of Stay in Patients Treated With and Without Growth Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEA Group</td>
</tr>
<tr>
<td></td>
<td>rhGH</td>
</tr>
<tr>
<td>Donor-Site healing time (days)</td>
<td>6.8 ± 0.07</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>149.6 ± 20.2</td>
</tr>
</tbody>
</table>

CEA, cultured epidermal autografts; rhGH, recombinant human growth hormone.
Data presented as mean ± SEM
CEA group results

Patients were grafted with CEA on post-burn day 30 ± 2.7. Two patients had en-block fascial excision, two patients had tangential excision, and three patients had a combination of both types of excisions performed in the first surgical procedure. A mean of a 44% ± 7% TBSA was covered with CEA, with an initial CEA take of 60% ± 8%. Fifty percent ± 8% of all areas covered with CEA needed to be autografted later in the acute hospital stay to achieve definitive coverage. We noticed no differences in take or re-grafting for anatomical distribution or age. When CEA take and re-grafting rates were compared in different burn-wound beds, CEA take was significantly better in fascial than tangentially excised wounds or engrafted dermis from allograft (78% vs. 45% take rate, p<0.001). Fascial excisions covered with CEA grafts, however, were more fragile and had a higher rate of blistering and re-grafting requirement (66% of re-grafting in fascial excision vs. 34% in tangential excision and allografts, p<0.001). Thus, dermal wounds, either autologous or homologous dermis, had the best final take of CEA.

Quality of scars and reconstructive procedures

Patients in the CEA group had a clinically more troublesome rehabilitation, although acute readmission for open wounds and rehabilitation problems were similar in both groups. Nevertheless, patients treated with CEA needed more reconstructive procedures in the first 2 years for functional problems (2.3 ± 1.4 vs. 0.9 ± 1.8, p=0.04). When the quality of scars was compared between groups, however, patients treated with CEA had scars with a significant smoother surface and less pigmentation than traditional meshed autografts, thus supporting the evidence that CEA grafts produce better cosmesis than widely expanded autografts. Border height and thickness were no different between groups (Table 4).

DISCUSSION

Culture epidermal autografting continues to be a controversial and expensive technique for the closure of burn wounds. The availability of cultured skin and clinical application were explored in the early 1980s. Initial reports were followed by larger series of patients treated with CEA, although short-term results have been inconsistent. Unsolved problems include patient selection, graft take, dermal replacement, and long-term durability.

Large cutaneous burns create acute physiological derangements and extensive cutaneous losses that, even in experienced hands, require repeated operations for debridement and grafting, creating a prolonged process for permanent coverage. The extent of the burn limits donor sites and increases the likelihood of burn wound sepsis, specially with delayed wound closure, which extends the period of metabolic stress and makes temporary burn wound coverage necessary. Under these circumstances, the advent and availability of cultured epithelial cells and the successful
Cost-efficacy of cultured epidermal autografts in massive pediatric burns

Table 4
Comparison of Burn Scars 2 years after the injury

<table>
<thead>
<tr>
<th></th>
<th>CEA group</th>
<th>Non-CEA group</th>
<th>Kappa test</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURFACE</td>
<td>2.5 (2-3)</td>
<td>3 (3-4) (*)</td>
<td>0.65</td>
</tr>
<tr>
<td>BORDER HEIGHT</td>
<td>3 (3-4)</td>
<td>3 (2-4)</td>
<td>0.45</td>
</tr>
<tr>
<td>THICKNESS</td>
<td>2.5 (2-3)</td>
<td>3 (2-4)</td>
<td>0.6</td>
</tr>
<tr>
<td>COLOR</td>
<td>2.5 (2-3)</td>
<td>3 (3-4) (*)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

CEA, cultured epidermal autografts.
Data presented as median and range
(*) p<0.05 Non-CEA vs. CEA group, Mann-Whitney rank sum test
Strength of inter-rater agreement (Kappa test):
- 0.61-0.80 = Good
- 0.81-1.00 = Very Good

Clinical application of such techniques in burned patients\textsuperscript{10,18-20} produced an initial enthusiasm for CEA among practitioners and gave rise to multiple clinical applications with short series and non-comparable data\textsuperscript{16}. Mean burn size in these patients averaged 60% TBSA\textsuperscript{4,11,12,17,19}, with different graft take and long-term results. Few clinical trials, however, comparing traditional techniques with CEA engrafting have been carried out. Munster et al\textsuperscript{12} found in their initial experience with CEA reduced rates of death and complications compared with an historical group. No significant variables in addition to CEA grafting were found that would explain this finding. Munster, in a prospective controlled trial\textsuperscript{4}, corroborated these findings with a significant reduction in the death rate in the CEA group. Drawbacks of these studies were the special patient selection and a mean burn size of 69% TBSA. The cost of care for CEA patients was significantly higher than for the control group, which brought into question the use of CEA in patients who could have had their wounds closed with an otherwise less expensive technique. This was also our experience. Patients treated with CEA incurred in higher hospital costs without significant decreases in the death or complication rate in this small series.

The use of total burn wound excision in the first 24 hours after admission and temporary wound closure with homografts has proved effective in reducing complications in severely burn victims\textsuperscript{3,21}. We believe that the use of this surgical approach in our patient population is primarily responsible for the low death rate in the patients who survived more than 30 days after the burn. Survival in the overall population with burns of more than 90% TBSA was also improved by this technique. More-
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over, Wolf et al\textsuperscript{1} determined that in massive pediatric burns, the major determinants of death are age, burn size, delayed resuscitation, and burn-associated sepsis or multiorgan failure; the type of surgical wound closure had no effect whatsoever. Patients with limited donor sites were also most apt to die in this study, but the effect of such a determinant in the current cohort of patients afflicted with burns of more than 90% TBSA must be very low. Although the ideal setting for CEA application may be for patients with near total loss of the skin (>90% TBSA, our experience and that of others emphasize current problems with CEA that must be solved for further application of this otherwise promising technique of tissue engineering.

Sheridan and Tompkins\textsuperscript{16} used CEA to treat five pediatric burn patients who had burns of more than 90% TBSA, with a successful initial engrafted rate (51\%) and delayed loss (60\%) similar to ours. They concluded that although CEA techniques played an important role in the management of massive burns, CEA should be limited to defined areas while the rest of the wound continues to be covered with traditional techniques. Rue et al\textsuperscript{22} also failed to identify any positive impact on wound closure in extensively burned patients, with a low long-term durability of such grafts. Initial take of CEA in our series was similar to others in the literature\textsuperscript{5,16}, and so were the areas blistered and regrafted with traditional autografts. The best take was on fascially excised wounds, but these areas were also those with the worst long-term durability. Our experience was similar to that of McAree et al\textsuperscript{17}: in their study, the best CEA initial take was on fascia (72\%), but deep dermal had the best average final take (95\%). The fragility of CEA during the initial postoperative period and a few months after discharge on fascially excised wounds makes these areas more prone to blistering and contractures\textsuperscript{4, 6, 16, 22}. It is also possible that some dermal wounds, although initially covered with CEA, may eventually heal by means of autogenous keratinocytes left in the dermal appendages, which would have greater inherent stability.

Patients treated with CEA in our cohort had similar rates of open wounds and readmissions, but the incidence of contractures and reconstructive procedures was significantly higher. Some of this increase in surgical procedures could be accounted for by additional coverage procedures for large areas initially closed with CEA grafts that were lost because of fragility, whereas the wounds in the group covered with conventional grafts responded to conservative wound management. In addition, the implementation of an active and aggressive rehabilitation program is subjectively troublesome and delayed because of the nature of the CEA graft and the tendency to blister under minimal mechanical trauma\textsuperscript{17}. Although as early as 6 days after surgery the epithelial graft has differentiated into a fully stratified epithelium with all four layers present in normal proportion, a basal lamina is not continuous until 4 weeks after grafting, and it is not until 5 months after grafting that the maturation is complete with a functional dermal-epidermal junction\textsuperscript{22}. Any minimal trauma, therefore, during this long maturation will provoke blisters and open wound formation, delaying the start and progression of the rehabilitation program. Therefore, we propose that these patients are inherently more prone to the development of contractures and
thus require more surgical intervention. The development and application of hydrophobic pressure garments have been proved beneficial in reducing surface maceration and shearing injuries\textsuperscript{24}, but the exact effect of such therapy in severely injured patients remains uncertain.

Other approaches that have been explored to improve the take, shorten the long-term fragility, and reduce the tendency to hypertrophy and contracture of CEA is the use of dermal equivalents. In fact, in our cohort of patients, deep dermal wounds and allografts had a significant better final take (although fascial wounds had the best initial take) than other wounds, which supports the notion that composite bioengineered skin would provide the best long-lasting wound closure.

Dermal replacement with engrafted allografts has been used effectively for dermal replacement\textsuperscript{5, 25}. Initial take consistently exceeded 80\%, producing a supple skin that was durable and resistant to trauma and infection. The problems and difficulties of initial engrafting and the removal of the alloepidermis made researchers search for new dermal equivalent that would provide long-lasting skin with an easier and quicker application. Types I and IV collagen, fibronectine, gelatine and laminine do not have an significant effect on growth and colony-forming efficiency, when included in extracellular matrices\textsuperscript{26}. However, when different substrates are combined to form an extracellular matrix, direct regeneration of normal skin morphology can be achieved. Collagen and chondroitin-6-sulfate\textsuperscript{27}, fibroblasts attached to collagen-glycosaminoglycan substrates\textsuperscript{28}, and cultured autologous keratinocytes with Integra (Johnson and Johnson, Arlington, TX)\textsuperscript{29} provide a dermal-epidermal junction and a quality of skin similar to that produced with traditional allografts engrafting techniques or with an acellular human dermis as dermal matrix (Alloderm, Life Cell, Newark, NJ)\textsuperscript{30}. The optimal dermal substitute, however, is still to be defined.

Despite the problems with long-term durability of the culture skin and the tendency for contractures, the cosmetic quality of scars in the CEA group appeared to be better than the control group. Given the fact that the control group comprised patients with burn wounds closed with conventional autografts, the assumption that the quality of scars in the conventional group would be better is defensible because of the presence of some dermis in the autograft. However, hypertrophy, thickness and raised surface were more obvious in the conventional group. An explanation lies in the long-term analysis of the wound covered with CEA, which shows eventual formation of a true dermis, unlike the interstices of meshed grafts, where this phenomenon seldom occurs. Five years after grafting, the underlying connective tissue has remodeled in a distinctly bilayered structure with collagen and elastic fibers and a vascular architecture resembling dermis\textsuperscript{23, 31}. The fact that widely expanded meshed grafts were used in the control group would explain the observation that patients grafted with CEA had smoother, thinner, and less pigmented scars.

In conclusion, in a prospective cohort of severely burned pediatric patients (> 90\% TBSA full-thickness burns), patients treated with CEA had a significantly longer LOS and higher hospital costs than patients treated with traditional widely meshed autografts. No differences in the death or complications rate were found.
between groups. Patients in both groups had similar rates of acute readmissions for open wounds, but patients in the CEA group had more contractures and reconstructive procedures. Patients treated with traditional techniques had more hypertrophic and hyperpigmented scars, whereas the CEA group had scars with better cosmesis.

Future research directions include determination of the optimal dermal replacement for cultured keratinocytes and shortening of the culture time. Tissue engineering techniques and cell transfection with cDNA coding for growth factors are also promising grounds of research. These developments would produce faster recovery with a shorter LOS and better long-lasting quality of bioengineered skin to permit the start of rehabilitation programs sooner and to decrease reconstructive needs.
REFERENCES