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Does the use of Integra®, an artificial dermal substitute, improve patient scar quality in burn injuries?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not Integra® improves patient scar quality compared to standard autograft-allograft technique or split-thickness skin graft (STSG).

Study Design: Selective EBM review of two randomized controlled trials and one retrospective study.

Data Sources: All studies were published in peer-reviewed journals found on PubMed.

Outcome(s) measured: The main outcome measured is patient scar quality, further defined by scar pigmentation, pliability, height, irregularity, vascularity, range of movement, softness, appearance, sensation, dryness, itch, and sweating.

Results: The study by Lagus, et al found that STSG had better scar outcomes than Integra® in 12 months. On the contrary, Branski, et al found a significant improvement in scars with the use of Integra® at both 12 months and 18-24 months post burn injury. The study by Moiemen, et al also showed statistical improvement in patient scars with Integra® two or more years after treatment.

Conclusions: The three studies evaluated in this EBM review have conflicting results. Further research is warranted to evaluate whether Integra® improves patient scar quality compared to STSG.

Key Words: burn treatment, Integra, skin grafting, dermal substitute

INTRODUCTION

Burns are defined as a traumatic injury to the skin and/or other tissues caused by extreme heat, electrical discharge, friction, chemicals, or radiation. They are further classified by the depth of the burn and the extent of the burn injury. Not only do burn injuries result in extensive tissue and organ damage, but they can also leave tremendous cosmetic defects. Although recent medical advances have greatly improved the morbidity and mortality of burn injuries, further research is still being conducted on ways to achieve better functional and cosmetic (scar) outcomes after a burn injury. This paper evaluates three studies that compare and evaluate two methods currently used in the treatment of burn injuries and aims to determine if one method is superior than the other.

Burn injuries are extremely common worldwide and in the United States. In fact, they are a global public health problem and are identified as the fourth most common type of trauma worldwide. [1] According to one systematic review, the average healthcare cost per burn patient is $88,218 (range: $704-$717,306; median $44,024).[1] In 2016, there were 486,000 burn injuries that received medical treatment and 40,000 hospitalizations in the United States.[2]

The usual methods used to treat burns include skin grafting, biosynthetic skin substitutes, Integra® dermal regeneration, tissue expansion, and flap reconstruction. Integra® was the first artificial skin substitute created to solve some of the shortcomings of skin grafting which include limited skin availability, susceptibility to infections, and high incidences of hypertrophic scarring.[3] Some studies claimed the superiority of Integra® over skin grafts, however, most of these claims were based on heterogenic studies and case reports.[3] The articles utilized in this selective EBM review include two Randomized Controlled Trials and one Retrospective Study

that aim to evaluate the effectiveness of Integra® in providing optimal cosmetic outcome versus skin grafts.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not Integra® improves patient scar quality compared to standard autograft-allograft technique or split-thickness skin graft (STSG).

METHODS

The population chosen for this review includes patients of all ages who have undergone treatment with Integra® post burn injury. The results from these patients were then compared against other patients or other sites that received standard autograft-allograft technique or split-thickness skin graft. The outcome that was measured is scar quality. This selective EBM review includes two (2) Randomized Controlled Trials and one (1) Retrospective Study.

Keywords used in searches include ‘Integra’, ‘burn treatment’, ‘skin grafting’, and ‘dermal substitute’. Each article used in this selective EBM is published data and written in English. All the research was done on PubMed and the articles were selected based on relevance to the clinical question. Inclusion criteria: relevant primary articles published between 2006-present that answer the clinical question. Exclusion criteria: articles that used a different method of treatment for burn injuries and articles that did not measure or evaluate patient cosmetic (scar) outcome after the use of Integra® post burn injury. Statistics reported or used include: P-value, SD, and/or mean change from baseline.

Table 1: Demographics & Characteristics of included studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Lagus[3] (2013)	RCT	10	17-70 yo	Age between 17 and 70 years; TBSA (total burned surface area) > 20%; Burns located on the anterior side of the body; Test areas were deep third-degree burns requiring fascial excision	None specified	2	Integra®, Cellonex, Split thickness skin graft
Branski[4] (2007)	RCT	20	Children (age range not specified)	Severely burned children admitted to the Shriners Hospital for Children in Galveston, TX between November 2001 and March 2003; Burn size ≥ 50% TBSA and ≥ 40% TBSA full-thickness burn; Patients admitted within 72 hrs of injury; Patients not septic at admission	None specified	1	Integra®, Standard autograft-allograft technique
Moiemen[5] (2011)	Retrospective Study	14	17-55yo	Fourteen (14) patients who had previously undergone standardized	None specified	0	Integra®

				two-stage scar resurfacing (reconstructio n) using Integra® more than 2 years before they were assessed; Patient ages between 17 – 55 years old			

OUTCOMES MEASURED

The outcome measured in this selective EBM review is the patient scar quality, further characterized by scar pigmentation, pliability, height, irregularity, and vascularity in two of the articles. In the third article, the patient scar quality was assessed based on range of movement, softness, appearance, sensation, dryness, itch, and sweating. Outcomes were measured in each article based on a scoring system as outlined in Table 2.

Table 2: Outcomes Scoring System

	Scoring System	**Outcomes Measured**	**Evaluator**	**Scoring Range**
Lagus, et al[3]	Vancouver Scar Scale	Scar pigmentation, pliability, height, vascularity	Occupational therapist	0 -13
Branski, et al[4]	Hamilton Burn Scar Scoring System	Scar height/thickness, irregularity, vascularity, pigmentation	Blinded clinicians	0 -14
Moiemen, et al[5]	Patient Satisfaction Questionnaire	Range of movement, softness, appearance, sensation, dryness, itch, sweating	Patient	-10 - +10

RESULTS

In the study by Lagus et al, the effectiveness of Integra® was compared against split thickness skin graft (STSG) and Cellonex (viscose cellulose sponge). Ten patients from the Helsinki Burn Center that met the inclusion criteria listed in Table 1 were chosen for the study. Each of the ten patients had three test areas: one area covered by STSG, a second area covered by Integra®, and a third area covered by Cellonex. The cosmetic outcomes of each test area were then evaluated 3 months and 12 months later by an occupational therapist using the Vancouver Scar Scale. The Vancouver Scar Scale has a scoring range of 0-13 and was specifically developed to measure pigmentation (0-2), pliability (0-5), height (0-3), and vascularity (0-3) of a scar post burn injury.[6]

Table 3: Vancouver Scar Scale[6]

	Scar Characteristic	Score
Vascularity	Normal Pink Red Purple	0 1 2 3
Pigmentation	Normal Hypopigmentation Hyperpigmentation	0 1 2
Pliability	Normal Supple Yielding Firm Ropes Contracture	0 1 2 3 4 5
Height	Flat <2mm 2-5mm >5mm	0 1 2 3
	Total Score	**13**

Data presented by the authors in the study by Lagus et al[3] include mean values and mean change between 3 and 12 months in scar vascularity, pigmentation, pliability, and height. For this

review, only the results for Integra® and STSG will be examined. Of note, in this study, lower scores equal better scar outcomes, as detailed in Table 3. In 3 months, STSG had a mean value of 1.3 in pigmentation, 0.7 in pliability, 0 in height, and 0.5 in vascularity. In 12 months, STSG scar pigmentation had a mean value of 0.4, pliability mean value of 0, height mean value 0.1, and vascularity mean value of 0.3.[3] These mean values show that in 12 months, test areas treated with STSG showed improvement in all categories, except for scar height.[3] On the contrary, in 3 months, Integra® had a mean value of 0.4 in pigmentation, 1.3 in pliability, 0 in height, and 0.8 in vascularity. In 12 months, Integra® scored a 0.4 in pigmentation, 0.4 in pliability, 0.1 in height, and 0.4 in vascularity.[3] Unlike STSG, in 12 months, Integra® only showed improvement in pliability and vascularity.[3] In regards to mean values of total scores, STSG showed improvement from 2.5 to 0.8 in 12 months, while Integra® had an overall improvement of 2.5 to 1.3 in 12 months. Overall, STSG scored better than Integra® in this study and found that Integra® did not perform better than STSG.[3]

Table 4: Mean values and mean change at 3 and 12 months[3]

	Pigmentation		Pliability		Height		Vascularity		Total scores	
	3 mos.	**12 mos**	**3 mos.**	**12 mos**	**3 mos.**	**12 mos**	**3 mos.**	**12 mos**	**3 mos**	**12 mos**
STSG	1.3	0.4	0.7	0	0	0.1	0.5	0.3	2.5	0.8
Integra	0.4	0.4	1.3	0.4	0	0.1	0.8	0.4	2.5	1.3

**P-values were not reported in this study.*

In the study by Branski et al[4], patients were randomized to receive either Integra® or STSG and respective burns scars were assessed using the Hamilton Burn-Scar Rating System. This scoring system is based on scar height/thickness, irregularity, vascularity, and pigmentation. The patient scars were photographed and assessed by blinded clinicians who were not involved in the care of the patients. The scars were evaluated at 12 months and again at 18-24 months post burn injury. Hamilton burns scar scores of Integra® was 5.4±1.7 at 12 months and 4.3±2.2 at 18-

24 months with a p-value of .035. On the contrary, Hamilton burn scar scores of STSG was 7.7±2.6 at 12 months and 6.6±3.1 at 18-24 months with a p-value of .403. Calculations were made using unpaired Student's t-tests (Kolmogorov-Smirnov test), clinical significance was accepted at $p < .05$ and statistical analysis were made using SigmaStat. Based on the assessments made by the blinded clinicians, this study concluded that there was a significant improvement in scars with the use of Integra® at both 12 months and 18-24 months post burn injury, while there was no statistical improvement in burn scars with STSG.

Table 5: Hamilton Burn Scar Scores at 12 months and 18-24 months after injury[4]

	Integra®	**Control**	***p*-value**
12 months	5.4±1.7	7.7±2.6	.003
18-24 months	4.3±2.2	6.6±3.1	.02
p-value	.035	.403	

In the study by Moiemen et al[5], fourteen patients who had previously received Integra® more than two years earlier were asked to assess their scars using a visual analogue scale via a patient questionnaire. The visual analogue scale ranged from -10 to +10, in which -10 represented deterioration, 0 represented no change, and +10 represented improvement. The patients scored their scars based on seven characteristics, including, range of movement, softness, appearance, sensation, dryness, itch, and sweating. Mean values and p-values are as listed below in Table 6. As shown in Table 6, there was statistical improvement (p-value <.05) with the use of Integra® in all categories except itch and sweating. The characteristics with the highest mean % improvement include range of movement, softness, and appearance (p-value <0.001) with mean % improvement of 39.2%, 44.6%, and 41.3% respectively. Sensation and dryness also showed statistical improvement with mean % improvement of 14.6% and 13.8%

and p-values 0.015 and 0.033 respectively. This statistical improvement supports the use of Integra® in achieving optimal scar outcomes.

Table 6: Patient's Self-Assessment of the Improvement of Their Scars with Mean Scores

	Mean % Improvement	p-value
Range of Movement	39.2	<0.001
Softness	44.6	<0.001
Appearance	41.3	<0.001
Sensation	14.6	0.015
Dryness	13.8	0.033
Itch	3.8	0.34
Sweating	0.00	1

DISCUSSION

For many years, split thickness skin grafting has been the standard of care in treating full thickness burns.[7] Over the past two decades, techniques in skin grafting have improved significantly from cutting grafts freehand with a large knife to the more current meshed split-thickness skin grafts harvested using a powered dermatome.[7] Recent studies have shown that the more recent skin grafting techniques appear to cause less keloid formation, contractures, and ulcerations than previous techniques, however, there are still many limiting factors to skin grafting, such as limited availability of native skin, risk of antigenicity with allografts, and poor cosmetic outcomes, which have led to significant interest in bioengineered skin substitutes over STSG.[7]

Integra® dermal regeneration template was one of the first bioengineered dermal substitute that showed promise in overcoming the shortcomings of skin grafting. Integra® is a bilayer dermal substitute with an outer layer and an inner layer. The outer layer consists of a polysiloxane polymer with properties that help control moisture, limit bacterial invasion, and provides protection against mechanical trauma.[4,7] The inner layer (dermal replacement) consists

of a highly porous scaffold made up of bovine collagen and chondroitin-6-sulfate, which helps facilitate dermis regeneration.[4,7] Although this dermal substitute has only been around for a few years, Integra® has seemed to successfully reduce hospital stays, improve patient's functional outcomes, and provide better cosmetic outcomes.[4] In this selective EBM review, two randomized controlled trials and one retrospective study were examined that compared the scar outcomes with the use of Integra® versus the standard split thickness skin graft.

In the study by Lagus et al[3], the authors concluded that Integra® did not provide better scar quality in comparison to STSG 12 months after Integra® placement. In fact, it performed the worst out of the three methods that were examined in the study. One reasoning for this that the authors alluded to is the possibility that the Integra® template maturation may not have yet been completed at 12 months and could have affected the results of the study.

The study by Branski et al[4], on the other hand, concluded that Integra® had better scar outcomes compared to STSG both at 12 months and 18-24 months post burn injury. This study also stated that only did Integra® have better outcomes at 12 months, but scarring actually improved significantly between 18-24 months after Integra® placement.

In the study performed by Moiemen et al[5], patients were analyzed two or more years after receiving Integra® treatment. These patients were given a patient satisfaction questionnaire which allowed the patients to self-assess their scars. The study concluded that there was significant statistical improvement in patient scar softness, appearance, range of movement, sensation, and dryness two or more years post Integra® placement.

In the three studies addressed in the selective review, small sample size is a shared limitation that could have affected the results and the validity of all three studies. There are also

differences in population demographics, severity of burn injuries, and assessment techniques in each of the studies, which could affect the generalizability of the data presented. Of note, searching for applicable and valid studies to be used for this selective review was also limited due to a very small number of prospective and randomized controlled studies available that examined long-term outcomes of Integra® as treatment for burn injuries.

CONCLUSION

The studies presented in this selective EBM review had conflicting results. One of the studies stated that Integra® does not improve patient scar outcomes compared to the standard STSG, while the other two studies concluded that Integra® performed better compared to the standard STSG. Of note, the two studies that concluded that Integra® improved patient scar outcomes evaluated patients 18-24+ months after treatment. In future studies, it might be worth evaluating a patient cohort who received treatment 18-24 months before assessment to ensure that the Integra® template has undergone full maturation before scar evaluation and identify if this influences results. Future studies should also include a patient cohort that are comparable with similar demographics and burn severity, ideally in a randomized controlled double blinded study.

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