Seven Years' Experience With Integra as a Reconstructive Tool

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The bilayered dermal substitute Integra (Integra Life Sciences Corp., Plainsboro, NJ) was developed and has been widely used as primary coverage for excised acute burns. Our take has been slightly different, finding it most useful in the management of complex soft-tissue loss and threatened extremities as the result of tendon, joint, or bone exposure. Often tasked to fill significant volume loss, we have become adept at stacked multiple-layer applications. Creative use of this material has resulted in unexpected successes with distal limb salvage; the technique takes its place beside adjacent tissue transfer, composite flaps, and vascular pedicle flaps in our burn reconstructive practice. A prospective registry (44 patients) has been kept during the past 7 years that catalogs wounds with complex soft-tissue loss treated with Integra grafts. Many of these patients were at risk of extremity loss because of exposed tendons, joints, or bone. Integra was applied after 1:1 meshing. With profound soft-tissue defects, multiple layers of Integra were serially applied 1 to 2 weeks apart for reconstitution of soft-tissue contours. Local Integra graft infections were managed by silicone unroofing followed by topical sulfamylon liquid dressings. Wounds addressed included fourth-degree burns, necrotizing fasciitis, pit-viper envenomations, and total abdominal wall avulsion in one patient after being run over by a bus. Patients generally were free of pain from their wounds during the maturation phase of the Integra neodermis. Restoration of tissue contour was significantly better when using multiple layers for deep defects. Second and third layers of Integra were successfully applied after an abbreviated first graft maturation period of 7 days. Epithelial autografts on multilayer Integra applications frequently "ghosted"; they would auto-digest to dispersed cells followed subsequently by the reappearance of a confluent epithelial layer. Final grafted skin morphology over palmar and plantar surfaces assumed the type and fingerprint pattern of the original tissues. Infections were readily visible. Early recognition kept them to easily treated circumscribed areas, which did not jeopardize the entire wound. Lengths of stay were long (range, 2–246 days) but not significantly greater than with traditional techniques. The specific reconstructive use of Integra permitted unexpected salvage of several threatened extremities by protecting exposed tendons, bones and joints. Long-term histologic examination revealed unexpected persistence of Integra collagen. Large volume loss wounds benefited from the ability to fill voids with multilayered applications. (J Burn Care Res 2007;28:120–126)

Despite great advances in the care of the burn patient, the management of complex injuries, such as those resulting from an electrical insult and those with exposed bone, tendons, and nerves, continues to be a challenging task for the burn surgeon. Although the rate of extremity loss after a burn remains relatively low at around 1.5%,[1] this rate increases to 32% to 79% when dealing with electrical injuries,[2–4] and between 18% and 40% when dealing with fourth-degree or circumferential extremity burns.[5,6] A recent report using a Comprehensive Urgent Reconstruction Alternative reported a

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decreased rate of extremity loss after an electrical injury of 9.8%; however, the amount of resources needed may make this approach difficult in most settings.[7] New, alternative methods for early covering of the complex burn wound are clearly desirable.

The "ideal" treatment for a particular patient should be tailored around his/her specific needs. In complex, fourth-degree burn wounds, the goals include coverage and protection of exposed tendons and bones, filling in deep soft-tissue defects, and preservation of function. To this end, a wealth of alternatives, including cultured epidermal autograft,[8] neurovascular pedicles,[9] muscle flaps,[10] and myocutaneous flaps have been described with varying degrees of success. In particular, techniques using flaps and pedicles are a technical challenge requiring multiple surgeries (a mean of eight in a recent report) and a mean length of stay of 76 days. They are associated with a flap failure rate of approximately 12% and an amputation rate of 18%.[11–13] Because of these shortcomings, the use of synthetic "scaffolds" to allow for native tissue regeneration continues to be an attractive alternative.

Integra (Integra Life Sciences Corp., Plainsboro, NJ) was approved by the Food and Drug Administration in 1996 for use in burn wound treatment. Its bilayered structure of bovine collagen plus glycosaminoglycan and silicone forms a neodermis that allows reconstitution of a full-thickness epidermis–dermis complex, theoretically improving grafting outcomes.[14] Although Integra initially was developed for the primary coverage of acute burns,[15] several authors have reported good experiences with its use in reconstructive surgery.[16,17] Because of the novelty of its "scaffold" approach, the timing and technical details of its application in acute burn wounds is still undergoing progressive refinement.[18]

Our experience with Integra began in 1998 and, since that time, we have kept a prospective photographic registry of the patients treated with it. Beyond straightforward burn wound closure, we surmised that it might have a reconstructive role and possibly help increase our limb salvage rates. In this report, we detail our 7-year experience using Integra as a reconstructive tool in fourth-degree extremity burns and the surprising persistence of Integra collagen evident in long-term histologic studies.

MATERIALS AND METHODS

Starting in October 1998, a photographic registry of patients has been kept to catalog wounds with complex soft-tissue loss that were treated with Integra grafts. We gathered data on 44 patients with fourth-degree burns in this time frame who were admitted to The Burn Center at Washington Hospital Center in Washington, DC. Detailed patient demographics, digital photography (including initial, midstream, and final results), and functional outcome have been prospectively collected. Our coauthors from Bridgeport, Connecticut, have maintained a similar registry, but with more comprehensive histological studies from tissue biopsies with 2 years' follow up.

The mechanism and severity (TBSA and depth of injury) were recorded for each patient. Wounds assessed included fourth-degree burns to the extremities, pit-viper envenomation, and, in one patient, total abdominal avulsion after being run over by a bus. We intentionally did not include any electrical injuries in this report because we believe they represent a very different population and thus will be discussed in a separate report.

After the 44 Integra patient cases were identified, we matched 44 control patients (from the same period of study) photographically by similar extent, depth, and location of injury. Patients in both groups were identified as being at risk for potential distal extremity loss because of the lack of viable soft-tissue coverage over tendons, joints, or bones upon presentation or after aggressive excision of nonviable soft tissues created large tissue defect (eg, secondary to necrotizing fasciitis).

Operative management of these wounds were planned and executed as per current practices. Patients in the control group had a combination of split- and full-thickness skin grafts, advancement, and rotational myocutaneous flaps. The possible use of Integra skin substitute was discussed with patients before surgery. The study patients had lntegra applied after 1:1 meshing in a noncrushing skin mesher (Brennen Med, St. Paul, MN) and covered with Acticoat (Smith & Nephew, London, United Kingdom) silver-impregnated antimicrobial dressing. Where soft-tissue defects were profound, serial applications (two or more) of Integra were used to build up the defects. All 88 patients in the study were treated by the same core group of three attending burn surgeons at the Washington Hospital Center.

Outcomes assessed with at least 1-year follow-up from time of discharge were amputations, length of stay, and cost per day; the latter two were extracted from our billing database. We used the Student's *t*-test for independent samples; a value of $P < .05$ was considered significant.

Our coauthors at the Andrew J. Panettieri Burn Center in Bridgeport, Connecticut, similarly apply multiple sequential layers in Integra when soft-tissue defects are profound. They contributed histology slides with both hematoxylin/eosin and Masson's tri-

chrome staining after a 2-year follow-up of the sacral region of a patient who suffered massive soft-tissue loss after a motorcycle crash and was immobilized by severe pelvic fractures. The Masson's tri-chrome technique stains mature collagen darker blue as is the characteristic in Integra's collagen and mature collagen in neodermis that has replaced Integra.

This particular patient was reconstructed with two layers of 1:1 meshed Integra. The first layer was applied with a wound vacuum system. After seven days, a second layer was applied, and 2 weeks later, the silicone layer was removed and an ultra thin split-thickness skin graft of 0.006 inches was applied. This measurement has been validated as the appropriate dermatome setting, which consistently obtains useful grafts.[19]

RESULTS

A total of 88 patients were treated with fourth-degree burns (or clinical equivalents), 44 each in case- and control-arms of the study. Of these, 16 patients in the control group and 35 in the Integra case group were deemed at risk for extremity loss based on fourth degree burns of at least one extremity. The other patients had fourth-degree burns involving the scalp, face, or torso.

There was a statistically significant difference in the amputation rates between the two groups ($P = 0.036$). The control group was par (31.5% amputation rate) with the historical controls in the literature that suggest amputations in 18% to 40% of patients. The Integra managed group suffered a 5.7% amputation rate.

The two groups were similar in terms of age and %TBSA. The control group had a mean age of 46.7 (range, 22–82 years) with a mean %TBSA of 16.1% (range, 4–56%) and the Integra managed group had a mean age of 37.9 (range, 15–73 years) and %TBSA 19.5% (range, 1–65%; Table 1). There was no difference between the groups in terms of length of stay (LOS) or cost per day (Table 1).

Table 1. Comparison of percent total body surface area burn (%TBSA), mean length of stay (LOS), mean cost per patient day, and amputation rate between Integra and the control group

	Integra	Control	Significance
Mean %TBSA	19.5	16.1	NS
Mean LOS	49.3	43.8	NS
Mean cost/day $	4318.93	4498.25	NS
Amputation rate	5.7	31.5	$P < .036$

Initially, grafts were held in postoperative dressings without manipulation or range of motion exercises for 72 hours. At 72 hours, the postoperative dressings were taken down, and dry sterile gauze dressings were used to protect the sites from soiling. As our experience increased, subsequent patients were successfully mobilized sooner and were participating in aggressive rehabilitation well before 72 hours postoperatively. Meshed lntegra grafts continued to receive Acticoat (Westaim Biomedical, Exeter, NH) dressings with sterile water application in the postoperative maturation period until final grafting with epithelial autografts on post-wound day 23 on average.

Frequently, the application of ultrathin epithelial grafts to the matured neodermis would demonstrate initial solid engraftment followed by progressive disappearance or "ghosting." This phenomenon has already been described by Fang et al,[19] particularly with skin grafts harvested at 0.002 to 0.004 inches. In our experience, this was always followed after 3 to 4 days by reappearance of a confluent epithelial surface and probably represents dispersal of the thin graft into individual cells or small aggregates of cells. Whether this is a manifestation of the (hypo) vascularity of our multiple layer approach and/or the vagaries of our local implementation of the Integra technique remains unclear.

Local Integra graft infections, typically less than 10 mm in diameter, appeared as subsilicone purulent collections during the 14-day neodermis maturation period. These were managed by sterile preparation of the sites followed by unroofing with Iris scissors. These wounds were then selectively treated with topical sulfamylon liquid or Acticoat antimicrobial dressings.

Five patients had defects that were deemed too deep for a single layer application of Integra to provide adequate coverage and contour. In these five patients, multiple layers of lntegra were applied serially to act as an "anlage" or scaffolding for reconstitution and sculpting of large volume soft tissue loss and coverage of vital deep structures (Table 2). Trichrome staining of tissue biopsies at 2-year follow-up shows mature collagen as dark blue staining (Figure 1A–D). In Figure 1A, we see a superficial section of the healed tissue and only a small area which shows the dark blue stain expected from the Integra. Figures 1B to D represent sequentially deeper sections with the unexpected finding of persistent, residual Integra. This shows that, contrary to the conventional belief, Integra may not be fully resorbed at 90 days. In this case, it seems to have persevered and may be a result of the multiple layer technique along with meshing

Table 2. Demographics and patient details on patients receiving multiple layers on Integra, including number of days in between applications and before final autograft of the index injury

Index Injury	Age	History	Time to Second Layer	Time to Autograft	Amputation
Tendon exposure left index finger	39	Copperhead bite	7	23	No
Third- and fourth-degree bilateral hands	43	Brush fire	8	36	Left hand and forearms
Third-degree right foot	32	Car accident, burst into flames, loss of consciousness	7	35	No
Fourth-degree left leg and foot tendon exposure	47	Tar burn	5	13	No
Fourth-degree both hands and fingers	38	Grease burn to both hands and all fingers	12	24	No

and subatmospheric pressure increasing the density of the dermal template.

The Following Case is Reviewed as a Representation of Our Experience

A 30-year-old woman was bitten in the right index finger by a pit viper (copperhead, *Agkistrodon contortrix*; Figure 2a). She was referred to our center for management of her necrotizing injury and after the initial débridment, 60% of the finger's circumference was lost (Figure 2b), creating a deep injury with exposed bone, joint capsule, and tendon. These injuries have been particularly difficult to manage because of the competing needs to quickly cover exposed bone, joint, and tendon while maintaining function and maximizing range of motion. A first layer of Integra was applied (Figure 2c); after maturation of the neodermis, the silicone layer was removed and a second layer was applied. Four months after the injury (Figure 2d), the original contour had been restored and matching fingerprints restituted. The patient did not loose any function of the distal interphalangeal joint, proximal interphalangeal joint, or metatarsophalangeal joints and regained 80% of the fingertip sensitivity to light touch.

DISCUSSION

The exposure of joints, tendons, and bones remains a major problem for soft-tissue surgeons. In response to this clinical challenge, several effective reconstructive measures have been developed, such as partial- and full-thickness skin grafts, local rotation flaps, pedicle advancement flaps, tissue expansion, and free vascular pedicle flaps. Nevertheless, extremity amputation continues to occur all too often.

This report details two burn centers' experience with multiple-layer application of Integra: 1) a 7-year experience using Integra as a reconstructive tool in the treatment of severe, fourth-degree burns, and 2) long-term histologic analysis of multiple-layer application.

The reported amputation rate decreased significantly with the addition of Integra to the armamentarium of techniques used to treat these difficult injuries. Although infection rate was not prospectively recorded in this report, one possibility for the observed reduction in amputations is that earlier dermal coverage of exposed tendons, bone, and joints might reduce the incidence of infection-induced necrosis in these marginally vascularized tissues. Furthermore, when an infection is present, it is easily seen, owing to the transparent nature of Integra; treatment often consisted of simple unroofing the silicone layer over the area of purulence, something not possible when a tissue flap is involved.

Surprisingly, the LOS did not increase significantly with the use of Integra for reconstruction. The first patients in the series did suffer a longer length of stay, partly because of overzealousness in "protecting" the fresh Integra grafts. These early patients had a completely restricted activity level for the first 72 hours after application. With more experience and confidence in the approach, we started mobilizing patients earlier, which helped to shorten overall LOS. The patient charges per day with Integra were slightly lower, although not significantly so, than the charges with the traditional methods. This was in part attributable to two patients in the control group who had tissue flap complications that eventually led to failure of the flap. There is at least one other report in the literature[20] that shows a decreased LOS with the use of Integra in the severely injured burn population.

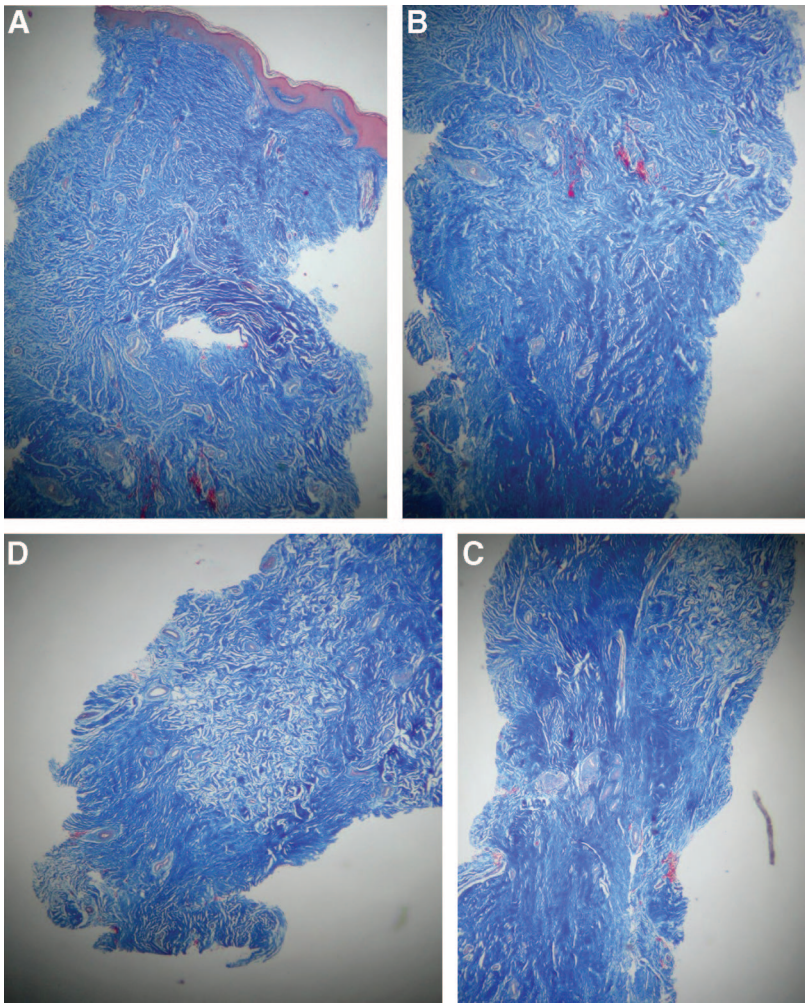

Figure 1. Clockwise from top left: A. Superficial biopsy showing mature collagen staining dark blue at the top right corner and recently formed collagen staining pale blue. The subsequent slides (B–D) represent sequentially deeper sections of the same tissue, showing a larger prevalence of mature collagen.

Although the initial learning curve has been steep, we have found several advantages with the use of Integra. First, the method uses an off-the-shelf tissue substitute. If an initial application fails or needs to be revised, no irreplaceable native tissue is lost. Furthermore, no muscular motor units or soft tissue are commandeered from their native purpose or location on the body. This material is simply brought onto the sterile field and applied.

Second, the technique allows for a significant degree of contour restoration after extensive tissue loss. Skin grafting is an inherently two-dimensional technique. Conversely, tissue flaps often are hindered by the excessive bulk of the donated soft tissue and can leave the donor area disproportionately hollow in relation to the contralateral side. We were able to selectively apply an inanimate biomaterial sheet, laminated in approximately 5-mm increments, which became a living, three-dimensional soft tissue graft of "custom sculpted" dimensions.

Third, some, but not all, patients faired well with pain control, rehabilitation, and quality of scar after Integra use in their reconstruction. However, patient response to these three parameters varied widely and probably represents a confluence of genetic predispositions and nuanced technical refinements we have yet to fully master. In the best circumstances, we observed that, after 1 year, scars appeared pliable, flexible, and smooth. In these instances, the use of Integra allowed not only unexpected limb salvage in some instances, but also more rapid restoration of function for the activities of daily living, ambulation, and return to gainful employment. This finding is consistent with other reports in the literature.[21]

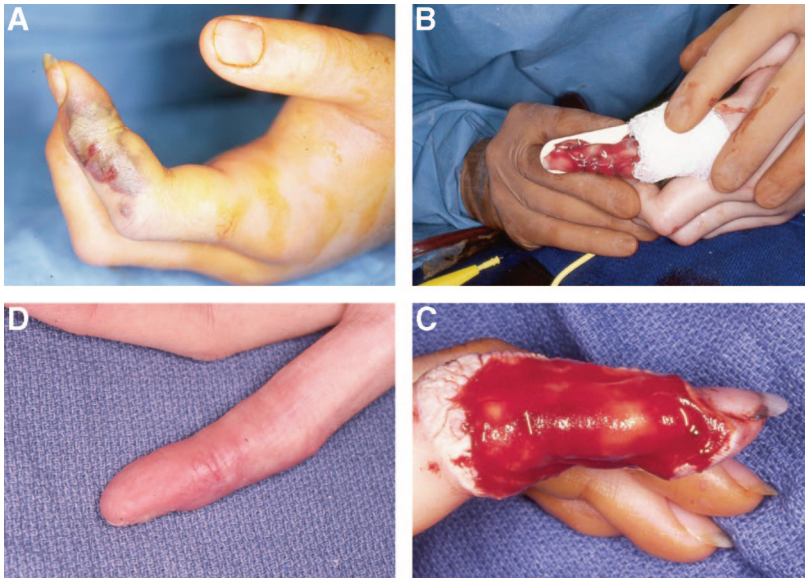

Figure 2. Clockwise from top left. Snake bite injury to the left index finger (A); after initial debridement (B) 60% of the finger's circumference was lost; (C) wound restoration with double layer Integra application; and (D) results at 4 months showing normal contour and even evidence of fingerprint pattern.

A precautionary note: Integra does not represent a panacea for all deep soft-tissue injuries. We believe use of Integra in some cases might be frankly disadvantageous, owing to the fact that this technique is inherently staged and requires at least two operations: one for application and a second to remove the silicone layer with placement of a subsequent thin skin graft. Not all injuries justify such a protracted (ie, expensive) approach. Patients with relatively small %TBSA burn, and those with more superficial burns, particularly if other co-morbidities that would make repeated intubation and anesthesia more risky, might benefit from a single-stage procedure.

Furthermore, the use of multiple layers of Integra should be seen as an unusual circumstance for cases of very deep tissue loss, and not the norm. Each individual application added approximately 5 mm of depth to the tissue, which in many instances is enough coverage for final grafting, thus saving the patient from further staged operations and earlier start of the rehabilitation phase. However, in very deep tissue loss or in certain situations in which cosmesis is important, a second or successive layers might be very worthwhile.

We believe Integra reconstruction has the potential to play a novel role, beside already-established techniques, in the treatment paradigm of fourth-degree burns. The persistence of Integra collagen on long-term histology was an unsuspected but intriguing finding. During the last 7 years, we believe it has allowed for some unexpected salvages of threatened extremities and permitted a modicum of soft-tissue sculpting via the filling of voids.

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