Three-year experience with Integra dermal regenerative template as a reconstructive tool

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Background
Since the introduction of Integra dermal regeneration template, several reports have been published worldwide proving its ability as a less invasive reconstructive tool. Our aim is to report our 3-year experience with Integra as the first report from Kuwait.
Patients and methods
Integra was used for reconstruction of a wide variety of complex wounds in different body locations. The dermal regenerative template replaced soft tissue defect as a first stage followed by skin grafting as a second stage. Forty patients were included with mean age of 40.2±20.7 years, with 24 cases having one or more comorbidities. Twenty-five patients were female and 15 were males. We had 20 cases with exposed underlying structures in wound bed, including bones, tendons, and joints.
Results
The average engraftment rate of Integra was 97±10.2%. Average time for skin grafting was 20.4±4.8 days and average skin graft take was 95±10.9%. Early complications included a case of Integra infection and another case of hematoma. After skin grafting, there were two cases of partial graft losses that healed without the need for regrafting. Complete wound healing was achieved in all cases within 8 weeks. Mean follow-up period was 16.65±8.4 months. No contracture or recurrent ulceration was documented. Apart from hyperpigmentation, 95% of the patients were satisfied with reconstruction outcome, with normal skin pliability in 95% cases, and normal range of movement in 85% of cases.
Conclusion
Integra is efficient and safe, with wide range of clinical indications. It has very high engraftment rate even in complex wounds with exposed bone or tendon. We observed high patient satisfaction and excellent pliability and final function.

Keywords:
complex wound, dermal regeneration template, Integra

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Introduction

Skin substitutes are heterogeneous group of biological and/or synthetic elements that enable the temporary or permanent occlusion of wounds. Although dermal substitutes can vary from skin xenografts or allografts to a combination of autologous keratinocytes over the dermal matrix, their common objective is to achieve the greatest possible similarity with the patient's skin [1,2].

Integra is a bilayer, permanent dermal regeneration template that is composed of dermal layer and temporary epidermal layer. The dermal matrix is composed of type 1 collagen (from bovine Achilles tendon) and shark cartilage. These materials are chemically cross-linked and then processed into a porous sponge referred to as CGM, collagen-GAG matrix. The silastic outer temporary layer is removed before skin grafting [3–5].

Since the introduction of Integra dermal regeneration template in 1996, several reports have been published from all over the world proving its ability to reduce both donor and graft site morbidity together with its ability to vascularize over small areas of exposed bone and tendon [6]. In this report, we presented our 3-year experience using Integra as a reconstructive tool for complex wounds.

Patients and methods

Patients

We used Integra (Integra Life Sciences Corp., Plainsboro, New Jersey, USA) for reconstruction of complex wounds in our institution from January 2014 to December 2016. We documented patient age, sex, comorbidities, wound etiology and location,

percentage of Integra engraftment, and skin graft timing and take. Both early and late complications were documented. Patient satisfaction and total period of follow-up were registered. All patients were formally consented after acceptance of the procedure from our institute ethical committee.

Surgical techniques

Cases were done by the same surgeons and were done either under local/regional/or general anesthesia according to size and location of the wound, taking into consideration patient comorbidities. This was a two-stage reconstruction, where Integra dermal regenerative template replaced soft tissue defect as a first stage followed by skin grafting as a second stage. In all cases, Integra was prepared in the same way in room temperature; 3 min soaking in antibiotic solution was done, followed by 1-min soaking in saline, then dried gently between two dry abdominal gauze using powder-free sterile gloves. No meshing was done; however, we made fenestrations by a surgical blade. Integra was applied to previously debrided viable wound bed with no signs of infection, and we ensured that perfect hemostasis was achieved. In all cases, Integra was fixed to the wound edges using surgical staplers or stiches depending on wound location. Integra dressing was done using nonadherent meshed dressing, silver-dressing sheet, and then sponge dressing connected to Negative Pressure Wound Therapy (NPWT). All NPWT machine modes were continuous mode with negative pressure of 100 mmHg. Integra was inspected in the third postoperative day, then once weekly while maintained dressed by NPWT. Once Integra showed adequate vascularization (usually by day 21 postoperatively), the outer silicon layer was removed, and split-thickness skin graft was applied. Skin grafts were dressed the same way used with Integra. Splints were applied if dealing with extremities wounds. Skin grafts were inspected on the fifth postoperative day, and then follow-up was planned at 1, 3, 6 months, then later every 6 months.

Table 1 Patient age, sex, and comorbidities

Variables	Value	%
Age (years)	40.2±20.7 (4–82)	
Sex		
Male	15	37.5
Female	25	62.5
Comorbidities		
Diabetes mellitus	12	30
Hypertension	8	20
Heavy smoker	8	20
Renal impairment	2	5
Immunosuppressive disease	1	2.5

Results

Integra was used in 40 patients to cover a wide variety of complex wounds. Table 1 shows patient demographics. Mean patients' age was 40.2±20.7 years (range, 4–82 years). Twenty-four (60%) cases had one or more comorbidities. Wound characteristics are summarized in Table 2. In 25 (62.5%) cases, wounds were caused by trauma, whereas 10 (25%) cases resulted from infection. In two cases, soft tissue defect resulted after burn contracture release, whereas we had soft tissue defect after neoplasm excision in two cases, and after keloid excision in one case.

In 24 (60%) cases, wounds affected the lower extremity, whereas in eight (20%) cases, wounds affected the upper extremity. The trunk was involved in four (10%) cases, whereas the head was involved in four (10%) cases. We had 20 (50%) cases with exposed underlying structures in wound bed. Eight cases had exposed bone only, whereas five cases had exposed tendon only. Combined exposure of bone and tendon was found in five cases and two cases had combined exposed bone/tendon/joint. Only 40% of cases underwent the procedures under general anesthesia. The remaining cases were performed under local/regional anesthesia.

The mean engraftment rate of Integra was 97±10.2%. Mean time for skin graft was 20.4±4.8 days (range, 14–40 days). The mean skin graft take was 95±10.9%.

Early complications were documented in two (5%) cases after the first-stage reconstruction. We had one (2.5%) cases of Integra infection and one (2.5%) case of hematoma. After the second-stage reconstruction, there were two (5%) cases of partial

Table 2 Wound characteristic

Item	*n* (%)
Wound etiology	
Post traumatic	25 (62.5)
Postinfection	10 (25)
Postneoplasm excision	2 (5)
Postburn contracture release	2 (5)
Postkeloid excision	1 (2.5)
Wound location	
Lower limb	24 (60)
Upper limb	8 (20)
Trunk	4 (10)
Head	4 (10)
Face	
Associated exposed structures	
Bone only	8 (20)
Tendon only	5 (12.5)
Bone and tendon	5 (12.5)
Bone, tendon, and joint	2 (5)

graft losses that healed without the need for regrafting. Complete wound healing was achieved in all cases within 8 weeks.

Mean follow-up period was 16.65±8.4 months (range, 1–36 months). We obtained normal skin pliability in 38 (95%) cases, and normal range of movement was achieved in 34 (85%) cases.

Regarding late complication, no contracture or recurrent ulceration was documented. The most common complaint was the hyperpigmentation, which is recorded in 40% of cases; however, 95% of the patients were satisfied with reconstruction outcome.

Figures 1–4 show examples of complex wounds of various causes and locations with excellent clinical outcomes, in the form of contour and skin pliability, and patient satisfaction.

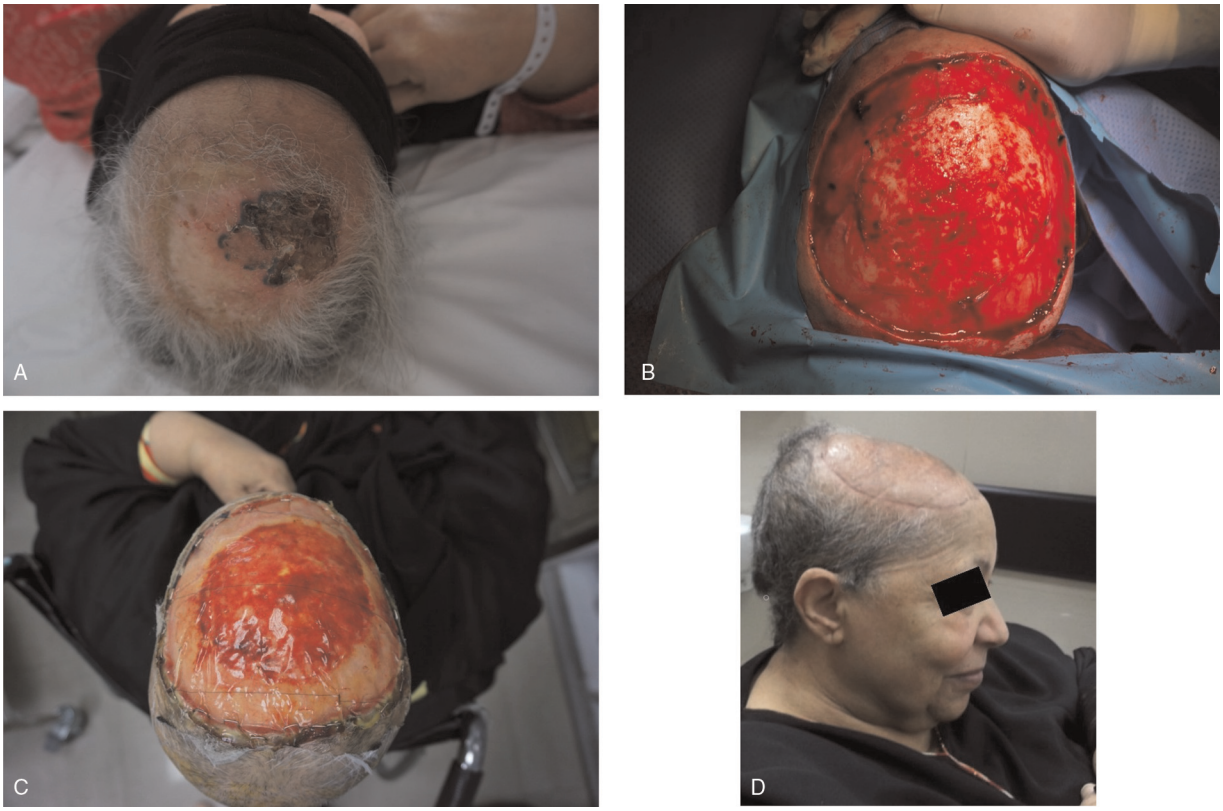
Discussion

Dermal regeneration template provides a novel element to add to the reconstructive tools used today by plastic surgeons [7]. In recent years, multiple studies and case reports have shown promising results with dermal substitute in both acute and chronic wounds.

In 1996, Integra was approved by the Food and Drug Administration for use in burn wound treatment. There are wide indication and reports in the clinical use of Integra for complex wound coverage. Dermal regeneration template has been used to resurface both hypertrophic scars and keloids with anecdotal success [7]. Integra has been used for resurfacing of postburn scars and contractures, diabetic foot ulcers and functional limb salvage [8], acute burns [9], traumatic degloving injuries [10], complex finger reconstruction [11], penis reconstruction following cancer resection [12], Fournier's gangrene [13], scalp defects after excision of malignant tumors [14], and exposed bone and exposed tendon [15,16]. In our experience, we used Integra in posttraumatic degloving injury, diabetic foot, necrotizing fasciitis, keloid, postburn contracture, and neoplastic lesion excisions.

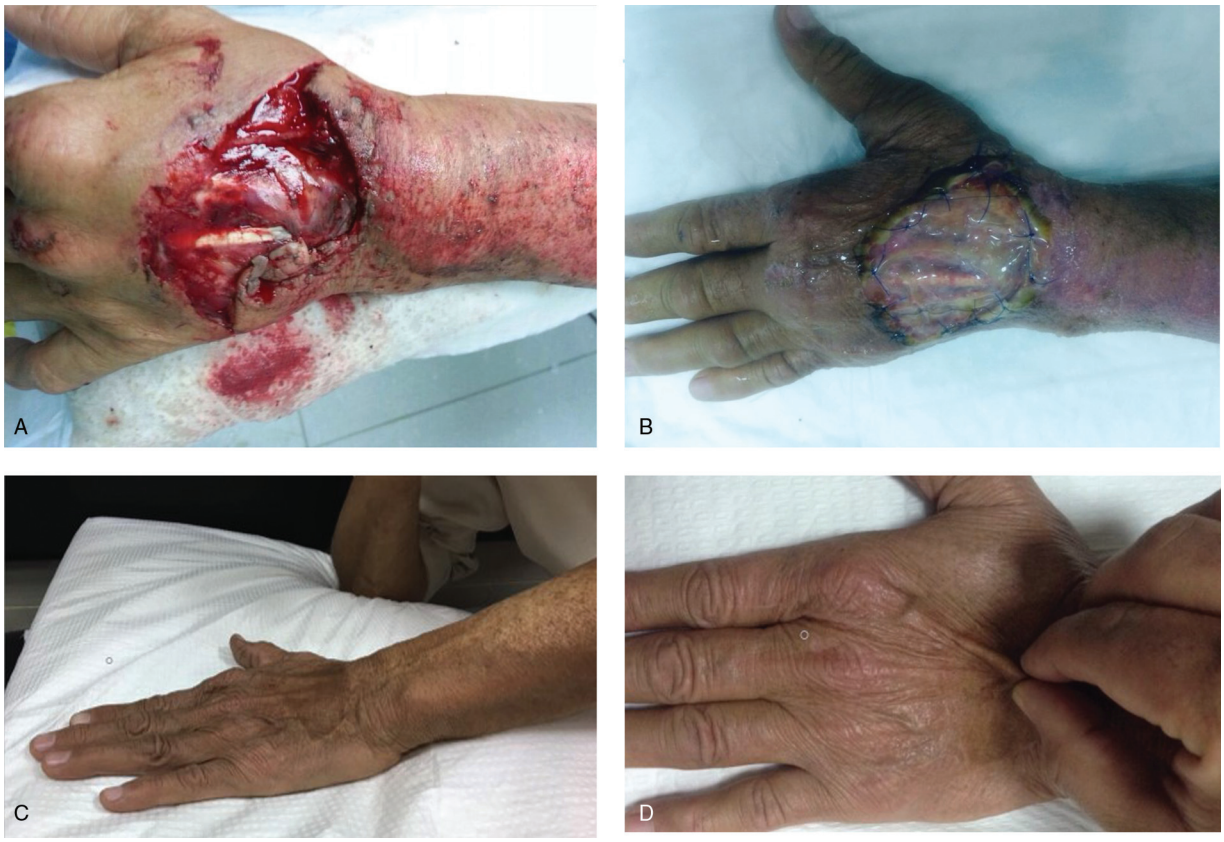
In our study, we had high success rates, although our patients were relatively old compared with most of the previous reports. Mean age of the patients was 40.2

Figure 1



A case of recurrent basal cell carcinoma (BCC) of the scalp. (a) Clinical presentation with ulceration and crusting with positive punch biopsy for BCC. (b) After surgical excision with safety margin including outer cortex with additional two inches excision of skin only to facilitate vascularization of the Integra sheet over exposed skull bone. (c) Integra 1 week after application. (d) Result after 1 year showing preserved contour.

Figure 2



Traumatic degloving injury of the dorsum of the left-hand. (a) At the time of trauma with deep laceration with exposed extensor tendons of the third and fourth digits. (b) 1 week after coverage with Integra. (c) Two years later showing excellent color match and preserved hand dorsum contour. (d) Excellent pliability of Integra/skin graft complex with free sliding of extensor tendons underneath.

±20.7 years. Adams *et al.* [17] had mean age of 49.5 years. Having older patients means dealing with more comorbidities and impaired wound healing process. Although 60% of our patients had comorbidities, our complication rate was 10%, and Integra engraftment and skin graft take were 97±10.2 and 95±10.9%, respectively, which is high compared with similar studies. Muangman *et al.* [4] had 98% Integra engraftment rate, with a very small number of patients (10 patients only) and 20% complication rate.

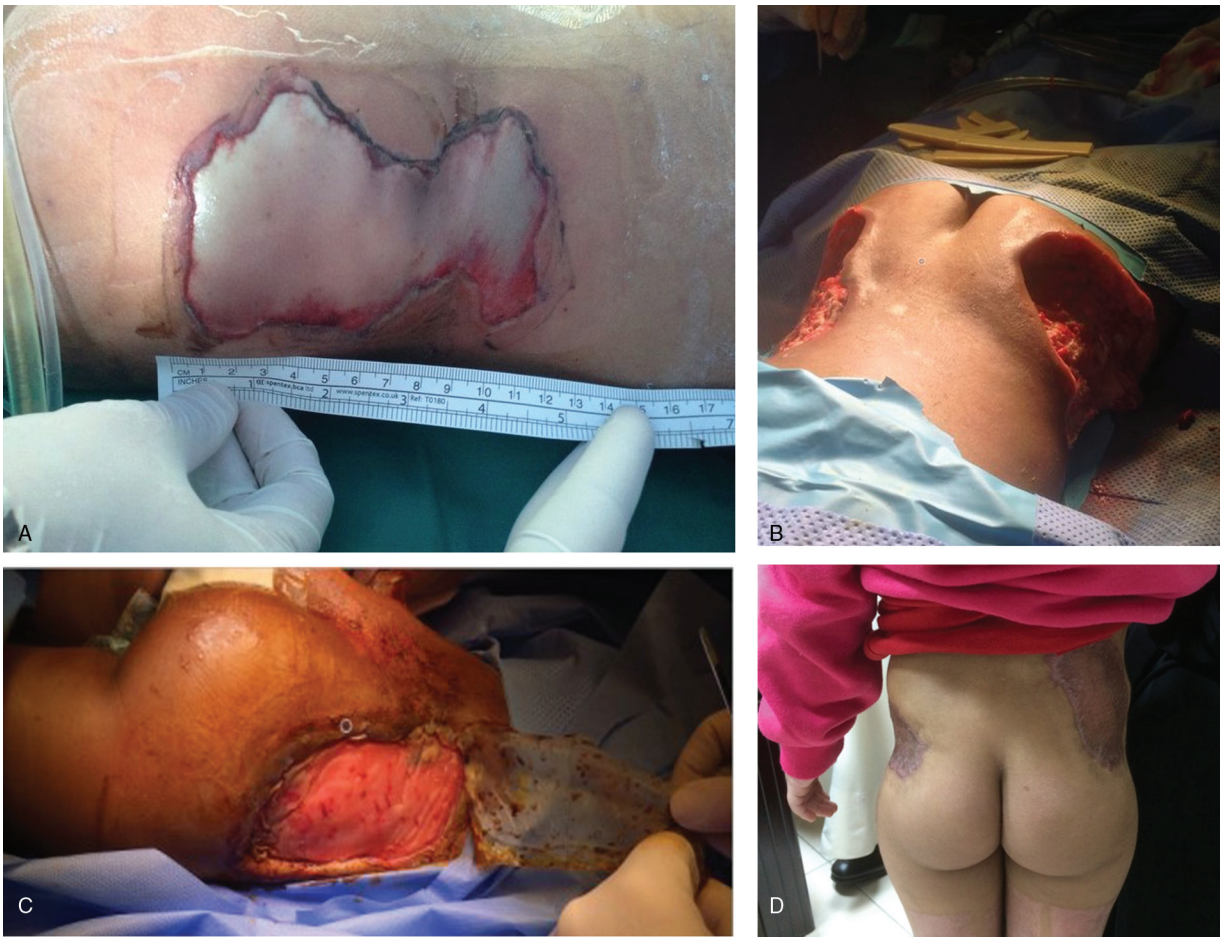
We used postoperative NPWT in all the cases to avoid shearing of the matrix off the wound and hematoma formation, and to aid Integra engraftment. In line with that, Molnar *et al.* [18] showed that application of subatmospheric pressure improved the take rate and time to vascularization of Integra, compared with previous published results, even with complicated wounds, with no adverse effects. Their estimated Integra take rate was 96% with 93% split-thickness graft take performed at 4–11 days (mean, 7.25 days). They had exposed bone in 62.5% of cases, joint in 50%, tendon in 37.5%, and bowel in 25% [18].

In our study, wound beds were associated with exposed structures (tendon, bone, joint, or combination) in 20 (50%) cases; however, we achieved 100% Integra engraftment rate in these cases. Problems occurred when there was a combination of three exposed nonvascularized structures. In the two cases with exposed bone/tendon/and joint, we had problems with the split-thickness skin graft take.

Second-stage surgery with application of split-thickness skin graft was done on average after 20.4±4.8 days from Integra application. Previous studies showed histopathological evidence of neovascularization by the third week [19]. However, in children, we had full vascularization of Integra template by day 14. All children had 100% Integra engraftment and skin graft take.

As for short-term complication, only four (10%) cases had minor complications. After Integra application, one case developed infection and another developed minor hematoma. The infected Integra was managed by de-roofing the silicon sheet and proper daily dressing with antiseptic dressing and 50% of

Figure 3



A child with chicken pox complicated with fatal *Varicella gangrenosa*. (a) She had bilateral full-thickness gangrene of the skin and subcutaneous tissue involving lower back posteriorly extending to both buttocks. (b) After surgical debridement. (c) Integra at time of silicone layer removal and skin grafting. (d) Two-year follow-up showing accepted wound closure.

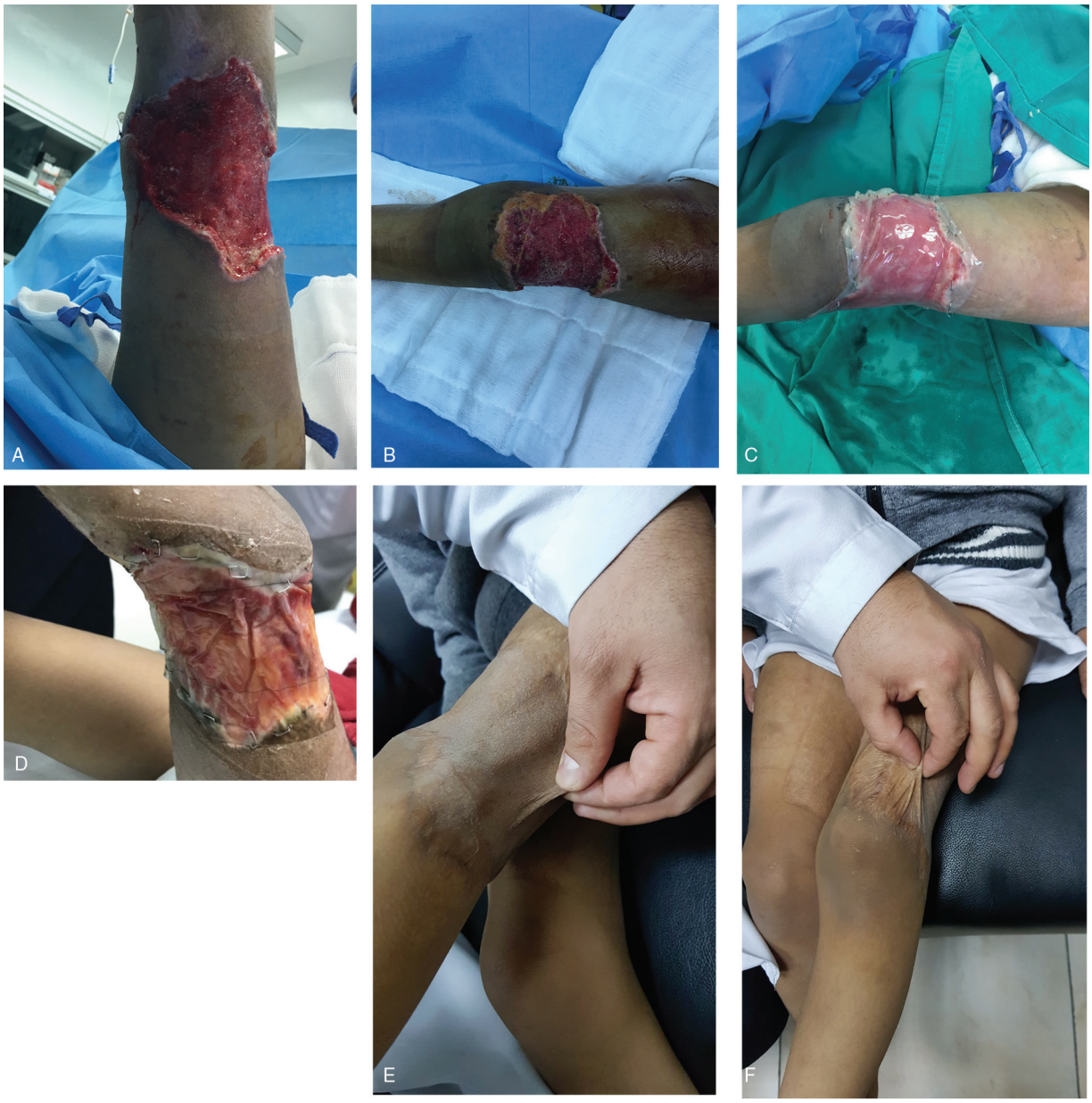
Integra template was salvaged. The case of hematoma was discovered at the same night of operation and was managed by irrigation through the manually made fenestration with 100% Integra engraftment at the end. After skin grafting, two cases developed partial graft losses that healed without needing regrafting.

Mean follow-up period was 16.65±8.4 months (range, 1–36 months). No serious long-term complication was found. No contracture, recurrent ulceration, or unacceptable scar was recorded. Many reports suggest that long-term results using dermal regeneration template lead to skin elasticity comparable to that of normal skin [7]. We achieved normal skin pliability in 95% of patients and normal range of movement in 85% of cases. The most common complaint was the hyperpigmentation (40%); however, most of patient (95%) accepted that, as they were informed preoperatively about the expected dark color of the scar.

To understand the tissue changes with Integra, Moiemen and colleagues conducted a clinical and histological analysis of patients treated with Integra dermal regeneration template more than 2 years earlier. They reported statistical improvement for range of movement, softness, and appearance; however, no statistical improvement of itching and sweating. Their histological analysis of the epidermis revealed reconstitution of Rete ridges in 70% of specimens. All specimens showed a degree of increased collagen fiber density in the reticular dermis. Three histological patterns of collagen were identified: nodular, parallel, and random. Elastic fibers were present in all specimens, and in 52% of specimen, there was evidence of nerve fiber regeneration limited to the middle or lower reticular dermis. There were no adnexal structures and no residual Integra matrix present in any specimens [19,20].

We reviewed the literature looking for similar case series reports in our region, and we found one pediatric case reported from Lebanon, which was managed as distal lower extremity traumatic wound using a dermal regeneration template and NPWT [21], and one case

Figure 4



A 3-year-old child with posttraumatic skin avulsion around the knee joint. (a and b) Surgical debridement of full-thickness gangrene of the skin and subcutaneous tissue involving anterior, lateral, and posterior aspects. (c) At time of Integra application. (d) After Integra engraftment at day of skin graft. (e and f) 30-month follow-up showing accepted scar color, normal skin pliability, and normal range of movement.

report from Malta of a patient who had failed pedicled transverse rectus abdominis myocutaneous (TRAM) flap and underwent chest wall reconstruction using omental flap and Integra [22]. By far, our paper represents the largest case series in the region.

Table 3 summarizes the comparison of current paper with previous published international papers [4,5,17,23–25].

Conclusions

We present data suggesting that Integra is efficient and safe, with wide range of clinical indications. Our experience showed that Integra has very high engraftment rate even in complex wounds with exposed bone or tendon. Nonetheless, we observed high patient satisfaction and excellent pliability and final function. Further large and well-designed prospective studies with longer follow-up period are needed to support our findings.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Table 3 Comparison of current paper with international papers

References	Design	Number	Age (mean)	Cause	Integra engraftment (%)	Follow up duration (years)	Complication (%)
Muangman *et al*. [4]	Retrospective	10	13–50 (32)	Variable	98	3	20 (infection)
Jeng *et al*. [23]	Prospective	44 (5 multiple)	15–73 (37.9)	Burn	NA	7	5.7 (amputation)
Lee *et al*. [24]	Retrospective	7	NA	Burn	71	2	28 (total loss replaced)
Stiefel *et al*. [25]	Retrospective	17 (pediatrics)	6.4–17.65 (13)	Hypertrophic scars and keloid	94	6	18 (infection and hematoma)
Adams *et al*. [17]	Retrospective	28 (from 3 centers)	14–85 (49.5)	Variable	86	6	21.7 (6.9% failure, 13.8% infection, and hematoma)
Lohana *et al*. [5]	Retrospective	23	4–73 (28)	Burn	87	4	8.7 (failure)
This article	Prospective	40	4–82 (40.2)	Variable	97	3	10 (1 infection, 1 hematoma, 2 partial graft loss)

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