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Review

Dermal regenerative matrix use in burn patients: A systematic review

Katie E. Hicks[a,*], **Minh NQ Huynh**[a], **Marc Jeschke**[b], **Claudia Malic**[c]

[a] *Faculty of Medicine, University of Ottawa, 451 Smyth Rd, K1H 8M5 Ottawa, ON, Canada*
[b] *Division of Plastic and Reconstructive Surgery, Department of Surgery, University of Toronto, Faculty of Medicine, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Room D704, M4N3M5 Toronto, ON, Canada*
[c] *Division of Plastic and Reconstructive Surgery, Department of Surgery, Faculty of Medicine, University of Ottawa, Children's Hospital of Eastern Ontario, 401 Smyth Road, K1H 8L1 Ottawa, ON, Canada*

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Summary *Background:* Dermal regenerative matrices (DRMs) have been used for several decades in the treatment of acute and reconstructive burn injury. The objective of this study was to perform a systematic review of the literature to assess clinical outcomes and safety profile of DRMs in full-thickness burn injury.
Methods: Comprehensive searches of MEDLINE, EMBASE, CINAHL, and Cochrane Library were performed from 1988 to 2017. Two independent reviewers completed preliminary and full-text screening of all articles. English-language articles reporting on DRM use in patients with full-thickness burn injury were included.
Results: Literature search generated 914 unique articles. Following screening, 203 articles were assessed for eligibility, and 72 met inclusion criteria for analysis. DRM was applied to1084 patients (74% acute burns, 26% burn reconstruction). Of the twelve studies that described changes in ROM, significant improvement was observed in 95% of reconstructive patients. The most frequently treated reconstructive sites were the neck, hand/wrist, lower extremity, and axilla. Vancouver scar scale was used in eight studies and indicated a significant improvement in the scar quality with DRM. The overall complication rate was 13%, most commonly infection, graft loss, hematoma formation, and contracture.
Conclusions: Although variability in functional and cosmetic outcomes was observed, DRM demonstrates improvements in ROM and scar appearance without objective regression.

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* Corresponding author.
E-mail addresses: khick086@uottawa.ca (K.E. Hicks), mhuyn095@uottawa.ca (M.N. Huynh), marc.jeschke@sunnybrook.ca (M. Jeschke), cmalic@cheo.on.ca (C. Malic).

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Essential demographic data were lacking in many studies, highlighting the need for future standardization of reporting outcomes in burns following application of dermal substitutes.

Contents

Introduction

Burn injuries represent one of the top causes of injury-related death, and its incidence varies worldwide.[1] Significant advancements in burn care over the past decades have led to improved patient survival and recovery, shifting the primary goal of management of severe burns from mere survival toward improving the "quality" of patient survival.[2,3] Quality of life largely depends on how patients reintegrate into the society, the scar quality and its appearance, and the perception of their own appearance. Autologous split thickness skin graft (STSG) is the current gold standard for the treatment of deep dermal and full thickness burn wounds[2,4]; however, there are numerous challenges associated with STSGs, including limited donor site availability, donor site morbidity, graft contracture, and an unpredictable or sometimes poor scarring process.[5,6] In addition to human allograft, epidermal and/or dermal biologic and synthetic skin substitutes have emerged in the last few decades.[5] Dermal regenerative matrices (DRMs) are permanent skin substitutes used in the management of skin defect after excision of burn wounds or release of burn wound contractures.

Developed in 1981 by Burke et al.[7], DRM (Integra, LifeSciences, Plainsboro, NJ, United States) is a bilayer dermal regeneration template composed of distinct dermal- and epidermal-like components. The dermal analog consists of cross-linked bovine collagen and shark chondroitin-6-sulfate, whereas the epidermal analog is composed of a thin silicone elastomer. After 2–3 weeks, a neodermis is formed, and the temporary silicone layer is removed and replaced with a thin epidermal autograft.[7,8] DRM is approved for use in acute burn surgery and burn reconstruction[9] and has been shown to produce excellent functional and esthetic results for both indications.[6,10-14]

In addition to its many benefits, DRM has also been cited to have several disadvantages, including the need for a two-stage procedure,[15-17] increased infection risk,[15,17] and high cost.[14,17] Although the literature is abundant with studies related to DRM use, most lack power of the sample and are mainly case series. The aim of this study was to perform a systematic literature review of DRM use and its outcomes related to functional improvement and scar appearance, when used in acute burn surgery and burn reconstruction for patients with full-thickness burn injury. A review of the safety and efficacy will also be performed.

Methods

Literature search and study selection

A systematic search of the literature was completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered with PROSPERO (CRD42018080191). Comprehensive searches of MEDLINE, EMBASE, CINAHL, and The Cochrane Library were performed during 1988–2017. Medical Subject Headings (MeSH) were used where appropriate. The search strategies for all databases are included in Table A1. English-language, primary full-text articles describing human subjects with full-thickness burn injury treated with DRM were included for analysis. Following the literature search,

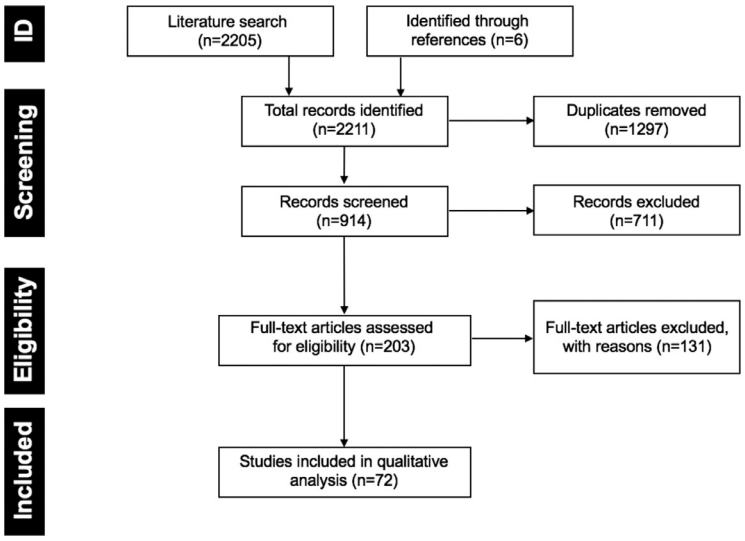

Figure 1 Flow diagram depicting the screening of articles for inclusion for qualitative analysis, reported in accordance with the Preferred Reporting Systems for Systematic Reviews and Meta-Analysis (PRISMA) statement.

duplicate citations were removed and preliminary screening (titles and abstracts) was performed to eliminate studies that did not meet the aforementioned eligibility criteria. Full-text articles were then obtained for all remaining studies, all of which were read in their entirety to identify relevant studies. Only articles that met all inclusion criteria were included for analysis. For the purpose of this systematic review, studies with insufficient information to extract data, review articles or animal studies, and for nonburn-related indications were excluded. Two independent reviewers completed preliminary and full-text screening of all articles.

Data extraction and analysis

Extracted data included study characteristics (design, year of publication, and authors affiliation), patient factors (demographics, extent of DRM reconstruction (% total body surface area [TBSA]), body regions affected, and mechanism of burn injury), surgical factors (acute vs. reconstructive indications and application technique), and clinical outcomes (scar appearance and cosmesis, biomechanics, functional range of motion, complications, and mortality). We defined the acute indications when DRM was used to resurface excised burn wounds during the initial admission after the thermal injury. Reconstructive burn surgery addresses functional and/or esthetic problems (e.g., burn contractures, hypertrophic, or keloid scars) that arise after all the burn wounds were treated and healed.[8]

Results

Study selection and characteristics

The systematic literature search generated 2205 articles, and an additional six were identified through article reference lists (Figure 1). After removal of duplicates, 914 unique articles remained for review. Following preliminary screening, 203 full-text articles were reviewed and 72 met inclusion criteria for data extraction and analysis.[2-6,8,10-75] Included studies consisted of four randomized controlled trials (Level 1), four comparative studies (Level 2), five cohort studies (Level 3), two case-control studies (Level 3), 24 case series (Level 4), and 33 case reports (Level 5). Most of the studies were from Europe and North America (Table 1).

Table 1 Authors' affiliation.

Continent	No. of studies	No. of acute cases	No. of reconstructive cases
Europe	37	107	216
North America	21	665	17
Asia	9	14	36
Australia/ Oceania	4	7	8
South America	1	7	7

Patient demographics

DRM was applied to 1084 patients with full-thickness burn injuries, mainly for resurfacing after debridement of acute burns (800 patients, 74%) and 284 for burn reconstruction (26.%). From cumulative data, there was a wide age range (7 months to 93 years), with 333 adult patients (≥18 years) and 179 pediatric patients (<18 years). Age was unreported for most patients (53%). Patient gender was available in only 56% of the cases (383 males and 221 females). The mean follow-up period for patients treated for acute burn injury and burn reconstruction was 21.8 and 21.1 months, respectively.

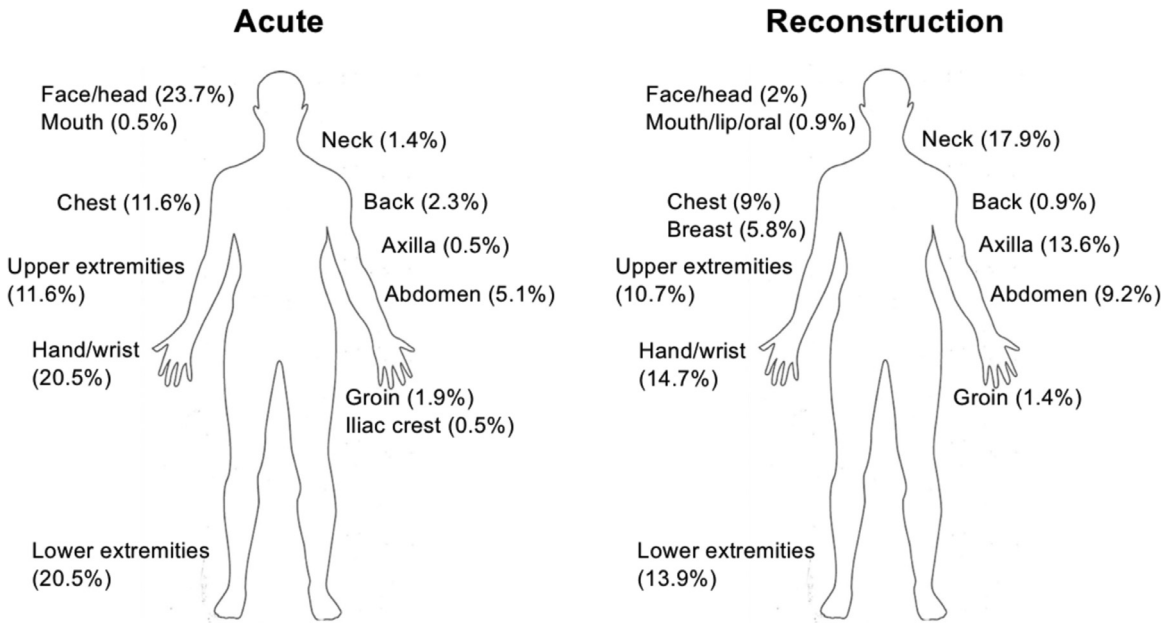

Figure 2 Anatomic distribution of DRM application for both acute and reconstructive indications; reported for 561 treated sites (48% of all DRM-treated sites).

Sites of DRM use

DRM was applied to a total of 1171 sites, covering a wide variety of body regions (Figure 2). The data lack accuracy in reporting what body regions were resurfaced, with only 48% of sites specified (215 sites for acute and 346 for burn reconstruction). The most commonly treated body parts for acute burn injury were face/head (24%), hand/wrist (21%), and lower extremities (21%). For burn reconstruction, the most commonly treated areas were neck (18%), hand/wrist (15%), lower extremities (14%), and axilla (14%).

It is important to assess how much of the DRM reaches readiness for skin grafting. The average DRM take for acute and reconstructive burn injuries was 86% (range 0–100%) and 95% (range 0–100%), respectively. STSG was applied over the DRM after 24.2 days (range 0–80 days), on average, with a 90% take for acute burns and 20.2 days (range 7–110 days) with 93% take for burn reconstruction. Cultured epidermal and keratinocyte autografts (CEA) were applied over DRM after 21 days, on average, (range 16–24 days).CEA was used alone for five patients[31,68,71] and was combined with a STSG for one patient.[45]

Function and range of movement-related outcomes

There was a wide range of reported outcomes related to function and range of motion (ROM). The improvements following DRM application were assessed with objective (four studies) or subjective methods (eight studies).

Objective outcomes related to function and ROM were reported in four studies for 42 patients, all of whom were treated with DRM for burn reconstruction.[8,11,18,19] Postoperative improvements were seen in 40 of the 42 patients (95%) (Table 2).

Subjective outcomes were reported in 111 patients from eight studies.[4,20-26] Ten patients were treated for acute burn injury and 101 for burn reconstruction. No improvement or temporary improvement in ROM was reported in 16% of DRM-treated sites.[23] Most patients had partial or significant improvements postoperatively, but minor limitations were still present in some (Table 3).

Scar-related outcomes

Three studies investigated the reconstructed tissue quality.[28,31,72] The average gross elasticity, elastic function, biological elasticity, and viscoelasticity among 21 DRM-treated sites were 0.40, 0.61, 0.82, and 0.69, respectively. No statistical differences in gross elasticity, elastic function, or biological elasticity were found between DRM-treated sites and healthy, unburned skin.[28,72] One study reported reduced elastic stretch and greater viscous stretch with meshed autograft on DRM, with no difference in total stretch. These differences were not significant when cultured skin substitutes were applied over DRM.[31]

Vancouver scar scale (VSS) is a standardized instrument used to evaluate subjective parameters (burn scars) in an objective way, where a high score correlates with a worse scar (minimum score: 0; maximum score: 13).The resultant scores are observer-dependent; thus, VSS is most valuable in identifying changes within an individual vs. between individuals. Slight alterations in the scoring system exist; for example, additional options in the height and pigmentation categories, which generate maximum possible scores of 14 and 15. These scar scales, among several other variations, are termed modified VSS.[76] Nine studies used scar scales to evaluate scar appearance in a total of 125 patients who had DRM applied for acute (69 patients) or reconstructive indications (56 patients).[2,6,8,10,18,27-30] The VSS was used in eight

Table 2 Functional outcome – range of motion (objective) (n=4).

Article	Body site	Outcome
Chou et al., 2001 (n=13)	Elbow	+30°, n=6
	Axilla	+65°, n=2
	Wrist	+31°, n=4
	Upper arm	+45°, n=1
Figus et al., 2007 (n=1)	Axilla	0°-30°→ 0°-120°
	Antecubital fossa	120°-160°→ 0°-160°
	Wrist	-160° to -140°→ -45° to +45°
	Neck	90° fixed flexion → 0°-90°
Moieman et al., 2001 (n=20)	Axilla, neck, groin, thigh, knee, foot, chest, back, abdomen, ankle, arm	Patients reported a 72% increase in ROM
Young et al., 2004 (n=8)	Wrist	"Excellent" results (75-100% ROM); n=5
	Axilla	"Good" results (50-74% ROM); n=1
	Elbow	"Poor" results (no change in ROM); n=2
		Wrist: 2 sites FFD (+15°, +20°)
		Elbow: 2 sites FFD (+55°, +90°)

*FFD=fixed flexion deformity

Table 3 Functional outcome – range of motion (subjective) (n=8).

Article	Acute/reconstruction (n=number of patients)	Outcome
Cedidi et al., 2002	Acute (n=1)	Functional ROM was complete and "excellent"
Verolino et al., 2008	Acute (n=1)	Normal mobility with right hand, good thumb opposition
		Active ROM was normal 2 years postop
		Active flexion of the IP joints was limited (5-15°)
		Passive motion quasi normal in flexion and extension for all IP and MP joints
Pontini et al., 2015	Acute (n=1)	Satisfactory oral ROM at 12 months
Frame et al., 2004	Reconstruction (n=89)	Post-treatment ROM (rated by *physicians*):
		Excellent (46%, 59 sites)
		Good (29%, 37 sites)
		Average (9%, 11 sites)
		Below average (16%, 20 sites)
		Post-treatment ROM (rated by *patients*): 86% satisfied
Popescu et al., 2007	Reconstruction (n=1)	Extension of neck was significantly improved
		Mouth opening was almost normal
Lynch et al., 2008	Reconstruction (n=1)	Contracture release improved the patient's neck ROM
Park et al., 2009	Reconstruction (n=3)	Significant improvement in shoulder abduction and extension
		Improved ROM
		Good ROM at ankle
Cuadra et al., 2012	Acute (n=7),	Range of articular motion was complete in 15/17 cases (88%)
	Reconstruction (n=7)	Moderate motility limitation in both active and passive movements of 5th digit; n=1
		Limited flexion of fingers; n=1

studies (original VSS in one, modified VSS in five, and unknown for two) and the remaining study used the Hamilton-burn scar score. Postoperative improvements in VSS score were seen in all reconstructive patients,[8,18,29,30] and ten acute patients (at 12 months vs. 3 months postoperatively).[2] For the remaining acute burn injury patients, two studies provided only one mean postoperative VSS score (2.08[28] and 3.10[30]) without earlier or later values for comparison. Only one study revealed a nonsignificant increase of the VSS score for the scars after DRM application, when compared with control sites (6 vs. 4).[27] The mean postoperative VSS score was higher in the reconstruction vs. acute burn injury group (4.7 vs. 2.3). The mean postoperative VSS score in control patients treated for acute burn injury was 2.9. No control subjects were available for comparison of postoperative VSS scores following burn reconstruction (Table 4).

Assessment of scar appearance and cosmesis was measured subjectively in thirty-six studies.[2,4,8,10-13,15,20,21,23-25,29-51] All studies reported good or improved esthetic outcomes in most patients. Suboptimal cosmetic outcomes were found for a subset of patients, including poor esthetic result (n=4),[10,15,37,40] pruritis,

Table 4 Scar cosmesis (scar scales) (n=9).

Article	Acute vs. Reconstruction (n=number of patients)	Outcome
Anderson et al., 2011	Acute (n=5 (DRM); n=8 (control))	Median VSS DRM: 6 Median VSS control (CEA +STSG): 4 *Not a significant difference
Branski et al., 2007	Acute (n=10)	Mean Hamilton-burn scar score: DRM: 4.2 Autograft-allograft (control): 6.6
Danin et al., 2012	Acute (n=22)	Mean VSS: 2.08
Lagus et al., 2013	Acute (n=10)	Mean ΔVSS: DRM: 2.5 → 1.3 STSG: 2.5 → 0.8 Cellonex: 2.9 → 0.8
Zajicek et al., 2017	Acute (n=11)	Mean VSS score: DRM: 1.4 DE graft (control): 4
Chou et al., 2001	Reconstruction (n=13)	Mean ΔVSS: 8.7 → 2.5
Moiemen et al., 2001	Reconstruction (n=20)	Mean ΔVSS: 13.3 → 9
Palao et al., 2003	Reconstruction (n=12)	Mean ΔVSS: 8.1 → 2.5
Dantzer et al., 2003	Acute (n=11), Reconstruction (n=11)	Acute: Mean VSS of 3.1 Reconstructive: Median ΔVSS from 10 → 2

dryness, and hyper- or hypopigmentation (n=3).[8,29,42] Less desirable cosmetic results were observed in 4.7% of patients (22 patients)[2,43] when compared to controls; however, these differences were not significant in ten patients. The incidence of "poor esthetic outcome" was 2.2% (10 patients).[10,15,37,40] Self-reported patient assessments were largely positive for both acute[10,12,21,30,33] and reconstructive[8,23-25,29,30,42,48] burn injuries. In one study of 106 acute burn surgery patients, 26% preferred the appearance of the DRM-treated sites, 64% found no difference, and only 10% preferred the control site (meshed autograft).[12] A visual analogue scale (VAS), where patients were asked to rate their overall satisfaction on a scale of 1-10, was used in two reconstructive studies,[8,29] with an average VAS score of 8 (range 6-9) reported in one study.[29] For the other study, the VAS revealed a 59% improvement in appearance compared to preoperative states.[8] The color match of DRM-treated sites was found to be comparable to normal skin for acute burn injury,[2,28,38,43,50] except for one study that revealed pronounced hypopigmentation and small regions of hyperpigmentation in one patient.[31] For burn reconstruction, two patients developed a sustained color mismatch.[40,42] Palao et al.[29] reported hyperpigmentation among all patients; however, this improved in all patients at long-term follow-up (12-18 months). All other studies revealed comparable pigmentation between DRM-treated sites and healthy skin.[8,24,40,42] Additionally, the majority of DRM-treated sites (>280) showed good or excellent texture match to autograft-treated sites, with the final skin being soft, supple, and pliable.[4,8,11-13,20,23,24,29,31,33,39-42,46,50] A subset of 22 acute burn patients developed thicker skin on DRM-treated hands compared to healthy, nonburned hands (1.6 mm vs. 1.18 mm); however, this was not a statistically significant difference.[28] Loss et al.[45] reported subjectively thicker skin for one patient treated for acute burn injury (compared to nonburned skin). Two other studies reported inferior postoperative tissue quality at DRM- vs. autograft-treated sites,[2,43] with one article reporting no statistical difference.[2]

Complications

Complications associated with DRM were reported in 56% of studies (n=40) for 144 patients out of the total 1084 patients (13%). The most frequent complication was infection (n=27), reported in fifty patients (4.6%) - 32 for acute burn injury, 17 for burn reconstruction, one unknown. Five of the twenty-seven studies did not report an exact number of patients that developed an infection; however, infection rates were reported in three of these studies, at 10%,[28] 17%,[52] and 20%.[23] The remaining two studies had either an unknown number[53] or a maximum of two patients developed infection.[54] On average, infection was reported to occur 22 days post burn (range 7-42). The organisms responsible were most commonly *Staphylococcus aureus* (including MRSA and ORSA) and *Pseudomonas aeruginosa*, and less frequently *Staphylococcus epidermidis, Enterococcus, Aspergillus, Candida, Acinetobacter, Bacillus coliforms, Enterobacter, Klebsiella pneumoniae*, and *Serratia marcescens*. Partial or total DRM, CEA, and STSG loss occurred in 22, 1, and 11 cases, respectively. Other complications observed included hematoma formation (n=11), contracture or recontracture (n=10), seroma formation (n=5), and hypertrophic scar (n=5). Ninety-two patients developed a complication other than infection (8.5%), but the information was scarce and insufficient for reporting.

Ten studies reported mortality data;[3,5,6,12,52,54-58] however, only nine provided the specific number of deaths for DRM-treated patients. Death occurred for 89 patients treated for acute burn injury and one patient treated for burn reconstruction. The overall mean mortality rate seen

among the nine studies was 30% (range 3.4–100%). The cause of death was revealed for a subset of patients (15 patients) and included etiologies related to the severity of burn injury, such as multiresistant infection and sepsis[5,6,56,58] (13 patients), inhalational injury[5] (one patient), and multiple organ failure[55] (one patient). Toxic shock syndrome was the cause of death for one patient.[58]

Safety of DRM use

Forty-nine studies commented on safety of DRM. Most authors agreed that DRM is safe to use on full-thickness burn injuries, where insufficient donor skin is available, both in the acute and reconstructive settings.[4,6,8,10,12,14,15,17,18,21,24,29-32,34-38,42-44,47,48,51,52,59,60] Authors also frequently commented that in acute burn surgery, DRM with autograft is capable of achieving functionally and esthetically similar results to that of autograft alone[12,31] or unburned skin.[2,4] Three studies preferred DRM vs. traditional options due to improved functional and cosmetic outcomes.[10,13,14] These statements were applicable to a variety of body sites[10,21-23,28-30,32,36,43,44,48,51,61] and age groups.[3,6,14,23,37,42,47,62]

For acute burn injury, two of the articles presented instances where application of DRM may be not be indicated, such as patients with multiple comorbidities, where anesthesia places them at higher risk for a two-stage procedure,[16] and eyelid burns.[43] When DRM is used for burn reconstruction, compliance with the treatment and adherence to frequent follow-ups are mandatory to achieve good results.[11,15] Additionally, several studies indicated that surgeon experience plays a role in the successful application of DRM.[5,6,23,33]

DRM application – tips and tricks

DRM received recommendations from 35% of articles (n=25) due to its improved effectiveness. There was variability in surgeon preference with respect to the use of meshed[13,25,26,40,42,43] vs. unmeshed DRM.[37] Several studies reinforced the importance of adequate immobilization of DRM on the recipient wound bed to ensure successful take.[15,30,35,40,47,51-53,62] Methods recommended include tie-over dressings (especially when applied over joints),[15] extensive hemostasis,[30] VAC dressings,[25,26,35,47,52,53,62] an outer Biobrane dressing,[51] and running sutures, single stiches, metal clips, K-wires, or conformed splints.[47] The importance of continuous wound care was also emphasized.[8,24,26,42,43] With respect to infection control, some authors recommended antiseptic compresses[56] and/or antimicrobial therapy.[55,56] Variability in the time to second-stage procedure was observed. Two studies suggested a 2-week interval between DRM and epidermal grafting procedures to reduce the risk of future hypertrophic scarring.[30,40] In contrast, two other studies recommended delaying the second-stage procedure until four weeks after initial DRM placement to ensure adequate vascularization.[8,29] The thickness of the STSG varied between 0.05 mm and 0.25 mm, with a mean of 0.16 mm.

Discussion

DRM is one of the several artificial skin substitutes available for wound coverage with indications in acute burn surgery and postburn reconstruction. The body of literature currently available on DRM use in burn injury is variable with respect to study design, sample size, and reported outcomes. Age and sex were not reported for almost half of the total number of patients included for analysis. The outcomes across studies are not standardized, and subjective measurements are more frequently described than objective ones, making it challenging to quantify postoperative improvement.

Among the 72 studies included for analysis, DRM was applied successfully and safely to a variety of body sites in both acute and reconstructive settings. The literature review supports the clinical use of DRM as a valid alternative in the burn reconstruction patients, both for its functional benefits as well as its apparent reduction of recontracture rates compared to available alternatives.

Of the twelve studies that commented on postoperative changes in ROM, only a minority of patients (<16%) were found to have suboptimal functional outcomes and none experienced loss of function. An important consideration that may limit postoperative improvement in ROM is the severity of the initial injury. Given that DRM is recommended in instances where autograft is scarce, often with full-thickness burns covering >40% TBSA;[6] the preoperative functional status of this patient population is likely to be quite limited. Thus, careful evaluation of a patient's preoperative morbidity is paramount when drawing postoperative conclusions.

With successful application and take, DRM can produce excellent cosmetic results.[12,21,30] The forty-five studies that commented on esthetic outcomes indicate positive and encouraging results in acute and reconstruction burn patients. With respect to color match, an important consideration is that the result is more dependent on the epidermal skin graft than the DRM; therefore, the area of the donor site was important. Other factors, such as time between first- and second-stage procedures, may also play a role in affecting postoperative coloration. It has been proposed that shortening the time to autografting from 14 days to 7–10 days in regions of high vascularity (e.g., the face) may reduce complications of hyperpigmentation due to faster neodermis formation.[43]

Invasive infection is the primary cause of death in the acute period following a burn injury, accounting for about 51% of mortality.[77] It is unknown whether the risk of infection with DRM is related mainly to its intrinsic properties or due to the patient population that it is applied to (severe, full-thickness burns). Although both factors likely contribute, the severity of initial injury no doubt has an impact on a patient's risk of developing an infection. In fact, one study included in our analysis was terminated early due to the high incidence of infection associated with DRM in patients with burns covering more than 45% TBSA.[5] Based on these results, Pham et al.[78] subsequently suggested that DRM may be better suited for patients with less extensive burn injuries. In contrast, numerous other studies included for analysis had a mean TBSA of >45% without reporting infection as a complication. Thus, further work to identify specific patients at risk of developing infection with

DRM is needed to help surgeons in effective clinical decision making.

The overall mortality observed among included studies was 8.3%, with a wide range of reported mortality rates among individual studies. Factors cited to have played a potential role in the death of patients were higher (than usual) multiresistant infection rates,[6] relative surgeon inexperience in handling DRM,[5,6] burn immunosuppression,[5] and surgical site infections due to seeding from distant sites.[5] Although unlikely, there exists the potential for patients to develop toxic shock syndrome following DRM application – a complication that carries a high mortality risk among burn patients.[58] Thus, burn care specialists must exercise caution when using DRMs, especially in non-life threatening situations. Strict adherence to infection control measures and prophylactic nasal mupirocin or chlorhexidine to reduce staphylococcal nasal carriage has been suggested to further reduce the likelihood of this outcome.[58] In addition, increasing surgeon experience with DRM is paramount in improving take and reducing infection rates, ultimately leading to reduced mortality among burn patients. In a retrospective review of 1665 acute burn injury patients, Ryan et al.[79] identified three risk factors associated with mortality: (1) age >60 years, (2) burn injury >40% TBSA, and (3) inhalational injury. In a separate study by Ryan et al.,[57] equivalent mortality rates were noted among the control and DRM groups (30%), despite the DRM-treated patients having more baseline risk factors for death (significantly higher incidence of inhalational injury and %TBSA burned).

Despite some inconsistency in preferred application techniques, several common themes were identified. Authors unanimously preferred the use of thin autograft during the second-stage procedure for improved cosmesis and emphasized the importance of adequate immobilization of DRM to the wound bed to improve take. Various methods for immobilization were reported, with a heavy emphasis on the use of VAC techniques. Surgeon's experience with DRM has a significant impact on patient outcome. Hence, to facilitate this, Malic et al.[9] have generated a nationwide protocol on wound healing and DRMs using expertise from several Canadian burn care specialists. Their expert panel has recommended certain minimum training requirements for surgeons without previous experience handling DRMs. A detailed protocol was also developed for reference, via nationwide specialist agreement. By applying the techniques recommended by those experienced with handling DRM in burn injury, one can expect substantial reductions in complication rates in the future.

Limitations and future directions

There are several limitations to this review. First, the quality of studies included for qualitative analysis was variable, with the majority being case series and case reports (79%). Consequently, this impacts the power of our conclusions. Second, there was inconsistency in reporting of demographic and outcome data among included studies, which complicated interpretation of the data and limited our ability to perform a meta-analysis. Among the four randomized controlled trials (RCTs), only two reported on objective measures of esthetic outcome[2,6] and only one commented subjectively.[12] None commented on functional outcome. Clearly, there is a need for future RCTs that document postoperative functional and cosmetic outcomes to better understand the role of DRM in full-thickness burn injuries. Third, the geographic distribution of articles included in this study was heavily skewed toward developed regions in North America and Europe (80.5%).This is likely attributable to its high cost and our analysis being restricted to include only English-language articles. Thus, this article is limited by preexclusion of data from other countries, wherein the outcomes associated with DRM are reported in other languages. Lastly, none of the included articles conducted a cost-benefit analysis of DRM. This analysis is important to investigate moving forward, given that a major limitation of DRM use is its significant cost – both the material itself, and the lengthy hospital stay that is often required following application. Such analyses would provide burn specialists with the concrete data necessary to make more informed treatment decisions when allocating their healthcare system's resources.

Conclusion

Since its introduction in 1981,[7] DRM has been successfully used for a variety of applications, mainly burn injury. The objective of this work was to perform a systematic review of the literature to assess the clinical efficacy and safety of DRM use in patients with full-thickness burn injury. This review demonstrated improved functional and esthetic outcomes among the majority of patients treated for acute burn injury as well as postburn reconstruction. Both minor and major complications were observed across included studies with low incidence. Infection was the most commonly cited complication. We believe that the benefits of DRM from a survival, functional, and cosmetic point of view outweigh the risks of the aforementioned potential complications. In concordance with previous reports, DRM can be safely applied both in the acute and reconstructive phases of burn injury, at a variety of anatomic regions. A focus should be placed on improving certain, modifiable factors – namely surgical expertise in handling DRM and post-operative patient compliance – to see further advancements in outcomes. Furthermore, high-level evidence studies with objective functional and cosmetic outcomes of DRM in burn injury are required to improve our understanding of expected patient outcomes and provide patients with tangible, realistic goals for recovery.

Declaration of Competing Interest

The authors have no personal, commercial, or financial conflicts of interest to disclose. None of the authors have a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

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APPENDICES

Table A1 Systematic search strategies of databases.

MEDLINE	EMBASE	CINAHL	The Cochrane Library
1. exp Burns/ 2. (thermal adj3 injur*).tw. 3. (burn or burns or burned or scald*).tw. 4. 1 or 2 or 3 5. Skin, Artificial/ 6. (artificial* adj3 skin).tw. (substitute adj3 skin).tw. 8. integra.tw. 9. 5 or 6 or 7 or 8 10. 4 and 9	1. burn/ 2. (thermal adj3 injur*).tw. 3. (burn or burns or burned or scald*).tw. 4. thermal injury/ 5. 1 or 2 or 3 or 4 6. artificial skin/ 7. (artificial* adj3 skin).tw. 8. (substitute adj3 skin).tw. 9. integra.tw. 10. 6 or 7 or 8 or 9 11. 5 and 10	((MH "Burns+") OR (burn OR burns OR burned OR scald*)) AND ((MH "Skin, Artificial") OR (integra) OR (skin substitute) OR (artificial skin))	1. burn.mp. 2. integra.mp. 3. artificial skin.mp. 4. skin substitute.mp. 5. 2 or 3 or 4 6. 1 and 5

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