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Biobrane, TransCyte, acute wounds, burns, tissue-engineering

Tissue-engineered temporary wound coverings. Important options for the clinician

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SUMMARY

Finding an ideal temporary wound dressing is challenging. Although TransCyte®, built on Biobrane®, offers many of the characteristics of the ideal wound dressing, and may have added benefits from the delivery of extra-cellular matrix (ECM) and growth factors to the wound, the downside of high cost and less convenient storage and usage are considerable barriers to its broader adoption. The low cost and established clinical utility of Biobrane sets the bar high for new products.

Overview of burns

When the famous bank robber Willie Sutton was asked why he robbed banks, he simply replied, “Because that’s where the money is” (1). It is not surprising then that the earliest focus for tissue-engineered skin products was in burns, because it was thought “that’s where the skin is needed.” Although the most obvious of uses, it is also the smallest of contemplated applications today.

Burns have traditionally been classified as first, second or third degree, depending upon depth. However, a more recent schema is as follows. Injury restricted to the epidermis is termed superficial (previously first degree). Burns involving the dermis are classified as partial thickness (previously second degree), and can be superficial or deep. Superficial partial thickness burns involve the papillary dermis, while deep partial thickness burns involve both the papillary and reticular dermal layers.

Burns extending through all layers of the dermis and through to subcutaneous tissue are termed full-thickness (previously third degree). A burn extending to muscle is termed full thickness with injury to underlying muscle (sometimes call fourth degree).

Deep partial-thickness and full-thickness burns invariably require autografting to achieve healing. In the case of severe burns, a temporary covering is often employed as a bridge to autografting. Allograft from cadaver skin has been the traditional choice for the temporary dressing of severe burns*. Any new product intended as a temporary dressing must be compared to

* Porcine xenografts are sometimes used as temporary wound coverings. Xenograft is rejected more quickly than allograft and otherwise has the same deficiencies as allograft
A more recent publication (McCaig LF, Burt CW. National Hospital Ambulatory Medical Care Survey: 2002 Emergency Department Summary. Advance data from vital and health statistics; no 340).

Tissue-engineered temporary wound coverings

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this standard. The immune suppression observed in severely burned patients prevents rapid rejection of allograft, but rejection ultimately occurs, typically within days to weeks, necessitating repeat allografting if the patient is not yet ready for autografting. It is important to note that the immunosuppressed state of the burn patient makes it impossible to generalize the use of allograft skin to other applications requiring temporary skin coverage. The advantages of allograft are tempered by variable supply, the possibility of disease transmission — though careful screening of donors substantially reduces this risk — and bleeding provoked upon removal.

A tissue-engineered biological dressing or other temporary covering as efficacious as cadaver skin would eliminate these problems, allowing delay of definitive autografting until sufficient graft is available. Even more desirable is a product that eliminates the need for autografting. In many applications, limited autograft availability necessitates maximizing the available resource in the form of thinner grafts in which the donor site can be reharvested sooner, meshing of the graft, and using cultured epidermal cells. If the method chosen (e.g. a very thin split-thickness-skin-graft) does not supply a solid dermal layer, wound contraction, scarring, and long-term disability can result.

Under best of circumstances, autografting creates a donor site, which is itself a site of potential infection and fluid loss. The donor site is generally a partial-thickness wound, but sometimes extends no deeper than the epidermis. Donor wounds are associated with pain, discomfort, fluid collection, and the ever-present possibility of infection. The use of tissue-engineered biological dressings may help eliminate or reduce donor site wounds, lead to more rapid donor site healing, and require fewer donor site recropping procedures. This can ultimately result in reduced length of hospital stay and more rapid patient rehabilitation. The use of these products can also eliminate the cost of allograft and, in some cases, the nursing costs associated with repeated dressing changes. A tissue-engineered product that can replace or complement autograft may result in improved functional and cosmetic outcomes, and reduced morbidity by elimination of the donor site. Tissue-engineered products may also be used in conjunction with meshed autograft, where it may result in reduced scarring and improved functionality.

Between 1985 and 1996, in the United States, age-specific fire and burn death rates declined 27–42 percent across all age groups (3). In 1997, fire-related deaths numbered 3,961, down 24% from 5,189 in 1989. This improvement is due largely to the decline in residential property fires, which fell 21% during this period, from 513,500 to 406,500 (4). Advances in care are thought to have contributed little over the past two decades. \( \text{LA}_50 \), the percentage of total body surface area burned at which half of the patients survive, improved only modestly between 1980 and 1990, and this trend is believed to have continued into the present (5). Most of the improvement in burn care observed over the past half century occurred between 1970 and 1980. During this period, \( \text{LA}_50 \) improved from under 40% to over 65%, due primarily to the introduction of early eschar excision, skin banks, total parenteral nutrition, and improved antibiotics. These improvements in burn care today — the unsatisfactory cosmetic and functional outcomes following full-thickness burn injuries.

Each year in the United States, 696,000* people visit the emergency room due to burns (7), resulting in 50,000 hospitalizations (8). The majority of these cases in which the burns are not extensive, do not pose a clinical challenge. These patients usually have sufficient healthy skin from which autograft can be harvested. However, often sufficient healthy material is unavailable for autograft or the added trauma of creating a donor wound cannot be tolerated.

According to the American Burn Association (9), the average size of a burn injury admitted to a burn center is about 14 percent of total body surface area (TBSA). Burns of 10 percent TBSA or less account for 54 percent of cases, while burns of 60 percent TBSA or greater account for just four percent of admissions. The subset of severely burn patients represents the most compelling application in burns for a tissue-engineered biological dressing that can serve as either permanent coverage or a bridge to autografting. There are also certain rare skin disorders, such as toxic epidermal necrolysis (TEN) and epidermolysis bullosa (EB), which conditions resemble those that result from severe burns. These, too, may benefit from the application of tissue-engineered biological dressings.

The ideal synthetic wound dressing or biologic skin substitute should have the following characteristics, enumerated for the most part by Pruitt and Levine more than twenty years ago (10) and added to by ourselves and others (11):

- absence of antigenicity
- tissue compatible
- absence of local or systemic toxicity
- impermeable to exogenous microorganisms
- water vapor transmission similar to normal skin
- rapid and sustained adherence to wound surface
- conformal to surface irregularities
- elastic to permit motion of underlying tissue
- resistant to linear and shear stresses
• tensile strength to resist fragmentation
• inhibition of wound surface flora and bacteria
• long shelf life, minimal storage requirements
• biodegradable (for permanent membranes)
• low cost
• minimize nursing care of wound
• minimize patient discomfort
• translucent properties to allow direct observation of healing
• reduce heal-time
• not increase rate of infection
• patient acceptance

Some products which are often thought of as dermal replacements, such as Biobrane® (see below), are indicated for partial-thickness wounds that do not require skin grafts. Though this patient population is larger than that of full-thickness injuries in terms of number of patients, it is also far more price sensitive as a number of alternative wound dressings are available. Expensive tissue-engineered products, such as TransCyte® and Integra Bilayer Matrix Wound Dressing® (Integra Life Sciences, Plainsboro, NJ), are far too expensive for this market, and regardless of clinical and technical attributes are unlikely to have a role in this indication.

In most cases, it is difficult to argue for the use of expensive products on donor sites when cheap and effective alternatives, such as conventional wound dressings and Biobrane, are readily available. In extensive burns, where donor sites must be harvested multiple times, a tissue-engineered biological dressing that promotes faster, higher-quality healing may be justified.

Biobrane

Biobrane, a product of Mylan Laboratories, Inc., is a biosynthetic wound dressing constructed of a silicone film bonded to a porcine collagen cross-linked nylon fabric. Developed by Woodroof (12), it has been commercially available since 1979. Blood and sera in the wound clot within the nylon matrix, biologically fixing the dressing in place until epithelialization occurs. Importantly, the outer silicone membrane acts to reduce water loss from the wound by evaporation. After healing, Biobrane must be removed, but as healing progresses the dressing naturally separates from the wound. It is available in various sizes ranging from 5 x 5 to 15 x 20 inches, as well as in a glove format (13, 12). Biobrane-L is, according to the manufacturer, a less complex nylon fabric for use when less aggressive adherence is required (14). It utilizes a lower weight monofilament thread resulting in a less complex matrix, thereby reducing adherence to the wound, as compared with the trifilament thread of Biobrane (15).

Most often, Biobrane is used to treat patients with partial-thickness burns, typically on an outpatient basis (16, 17). It is best reserved for relatively fresh wounds (<24-48 hours), with low bacterial counts, and without eschar or debris, as Biobrane does not debride dead tissue (18, 19). In a controlled, non-blinded, 52-subject clinical trial in partial-thickness burns, Biobrane was shown to decrease total healing time by 29% (10.6 days vs. 15.0 days), lower treatment cost ($434 vs. $504), and reduce patient pain (1.6 vs. 3.6 out of 5) and use of pain medication (0.6 vs. 3.0 tablets) at 24 hours, with no significant change in the rate of infection as compared with the twice daily use of 1% silver sulfadiazine, an antimicrobial, covered with dry gauze and elastic wraps (15). In a controlled, non-blinded, 30-subject clinical study in patients with partial-thickness scald burns the use of Biobrane was also associated with decreased pain, reduced hospital stay, and reduced days of physical therapy (20). But not all studies are positive. A controlled, non-blinded, 49-subject clinical trial in partial-thickness burns failed to show an advantage to Biobrane versus silver sulfadiazine in reducing length of hospital stay (9.1 days vs. 9.2 days) or costs ($360 vs. $510), (21). Twelve percent of the Biobrane treated patients required early removal of the product, one case due to increasing burn depth and three cases for infection.

There has been some concern that Biobrane is associated with an increased risk of infection. In one 21-subject donor site study the infection rate was 57% with Biobrane versus 9.5% with Scarlet Red, the standard for treatment in the 1980’s (22). Others trials did not find an increased rate of infection. In a controlled, non-blinded 89 patient study in pediatric patients with superficial burns of less than 25% TBSA, its use was not associated with a greater incidence of infection when applied within 48 hours of injury (23). As in other studies, Biobrane use resulted in shorter hospitalizations and decreased healing time versus topical antimicrobials and dressing changes. In a 20-subject pediatric study in patients with partial-thickness burns presenting within 24 hours of injury, Biobrane was superior to 1% silver sulfadiazine and standard wound care on measures of length of hospital stay (1.5 vs. 3.6 days), time to complete wound healing (0.7 vs. 16.1 days), and use of pain medication (0.5 vs. 1.9 doses/person/day), also with no difference in the rate of infection (zero in both groups) (24).

Although some early studies concluded that as a temporary dressing Biobrane is as effective as frozen allograft in freshly excised full-thickness burn wounds (25), it is now considered that accurate diagnosis of wound depth and careful wound selection is considered critical as deep wounds interfere with Biobrane adherence (16, 17, 26). Often it is difficult to judge initially the depth of the wound, leading to nonadherence (27).

Out of a series of 201 Biobrane applications in four different clinical indications, 124 (61.7%) were left in
place until healing occurred, but the rates varied considerably by wound type, from 100% for shallow wounds awaiting epithelialization to 21.7% for deep wounds after eschar excision (28). Biobrane has little utility in deep partial-thickness and full-thickness burns other than as a dressing for meshed autograft (29), with removal at 5-7 days to allow for reepithelialization (24). But others consider it inferior to allograft for this application (30). The use of Biobrane-L, with less adherence, may be preferred for covering meshed autograft (13). Misuse may also contribute to infection, likely secondary to partial nonadherence and resultant bacterial proliferation. In a series of 141 pediatric scald burn patients, of which 106 were treated with Biobrane, there was a 22.6% infection rate which the authors attribute to inadherence (30). The use of Biobrane-L, with less adherence, may be preferred for covering meshed autograft (13).

Biobrane offers many of the characteristics of the ideal wound dressing described above. Importantly, wound desiccation is prevented and pain is decreased. Since dressing changes are performed less frequently, outpatient care is sometimes made possible, reducing hospital costs. It is also transparent, allowing direct wound observation. It is highly effective as a dressing for superficial partial-thickness burns, donor sites, and TEN. It is equivalent to or superior to silver sulfadiazine or xeroform gauze on most parameters and far preferred for patient comfort (24). Biobrane has no special storage requirements and a long shelf life. It handles well, with high elasticity and 100% elongation in any direction (9), but may be difficult to use in areas of irregular topography or on joint surfaces, though some have reported good results using meshed Biobrane even in these challenging areas (51). The risk of infection in inappropriately chosen wounds is the largest concern, followed by non-adherence, though initial non-adherence in a non-infected wound can be addressed with aspiration or reapplication. Although reported, hypersensitivity reactions to Biobrane have occurred on repeat application (52).

At Biobrane’s price of approximately £0.48 per sq. cm (53), it does not seem likely that any of the newer biological skin substitutes will prove more cost-effective or provide better outcomes in superficial partial-thickness burns.

**TransCyte**

TransCyte, originally termed Dermagraft-TC, was commercialized by Advanced Tissue Sciences, Inc. and is now a product of Smith & Nephew. It is composed of human neonatal fibroblasts cultured under aseptic conditions onto the nylon mesh component of Biobrane (54). The fibroblasts secrete into the mesh extracellular matrix components, such as fibronectin, type I collagen, decorin and matrix bound growth factors, but are themselves no longer viable in the final product (52). The presentation of the ECM components and the bound growth factors are thought to promote wound healing. The product must be stored between -20° and -70° C, and thawed at 37° C prior to use. It has a shelf life of 18 months at the proper temperature.

TransCyte received FDA approval in March 1997 for use as a temporary wound covering for surgically excised full-thickness and deep partial-thickness ther-
mal burn wounds in patients that require a covering prior to autograft placement.

Early studies in 10 adult burn patients indicated that TransCyte was at least equivalent to human cadaver allograft skin (55). The initial approval was based upon a 66-patient trial in which comparable full-thickness or deep partial-thickness burn sites on each patient were randomized to receive either TransCyte or cadaver allograft. TransCyte sites, when evaluated 14 days post-autograft, were equivalent to or superior to allograft with regard to ultimate autograft take: 94.7% vs. 93.1% (56). TransCyte also performed better than control on secondary endpoints such as ease of removal, degree of excision required, amount of bleeding upon excision, and overall satisfaction rating by investigators (54). TransCyte was equivalent to control on the secondary endpoints of adherence, wound closure, and infection (54).

In October 1997, TransCyte’s label was expanded to include partial-thickness burns that are mid-dermal to indeterminate depth and that may be expected to heal without autografting. In a 14-subject, randomized, within-patient paired comparison study, the one-time application of TransCyte resulted in a 39% decrease in time to 90% or greater epithelialization versus silver sulfadiazine cream applied with once or twice-daily dressing changes: 11.1 days vs. 18.1 days (57, 58). The use of TransCyte also resulted in significantly less hypertrophic scarring, as defined by the Vancouver Burn Scar Scale, versus control (55). It is little surprise that the TransCyte performed better than a silver sulfadiazine control in partial-thickness burns. Biobrane, the nylon mesh base of the product, itself performed better than silver sulfadiazine in clinical trials (see above).

In a 21 patient study comparing TransCyte with standard topical antibiotic management in adult patients with mid-dermal facial burns, there was a decrease in wound care time (0.35 vs. 1.9 hours), pain (2 vs. 4), and time for reepithelialization (7 vs. 13 days) in the TransCyte group (57). The use of TransCyte also resulted in significantly less hypertrophic scarring, as defined by the Vancouver Burn Scar Scale, versus control (55). It is little surprise that the TransCyte performed better than a silver sulfadiazine control in partial-thickness burns. Biobrane, the nylon mesh base of the product, itself performed better than silver sulfadiazine in clinical trials (see above).

In a series of 20 pediatric burn patients treated with TransCyte, compared with an historical control of 20 pediatric patient treated with antimicrobial ointments and hydrodebridement, only one child (5%) in the TransCyte group required autografting as compared with seven children (35%) in the control group. The TransCyte treated group had decreased hospital length of stay versus control: 5.9 vs. 13.8 days (60).

In a randomized 33 patient, 58 wound site study directly comparing the effectiveness of TransCyte, Biobrane, and Silvazine cream (silver sulfadiazine and 0.2% chlorhexidine) in treating children with partial-thickness burns, the mean time to 90% of greater reepithelialization was 7.5 days for TransCyte versus 9.5 days for Biobrane and 11.2 days for Silvazine. The percentage of wounds ultimately requiring autografting were only 5% for TransCyte as compared with 24% for Silvazine, and 17% for Biobrane. TransCyte-dressed wounds required fewer dressing changes (1.5) than either Biobrane (2.4) or Silvazine (9.2) (59).

At £7.87/sqr. cm TransCyte is 16-times more expensive than Biobrane, 2.3 times more expensive than Integra Bilayer Matrix Wound Dressing, and 13 times more expensive than allograft (51). It is also more difficult to store and handle than either of the above synthetic products. This higher cost versus allograft may be justified based upon the latter’s limited availability, the risk of viral transmission by cadaver skin, and TransCyte’s advantages on the secondary endpoints described above (54).

TransCyte, in its pivotal clinical trial (54), was used in full-thickness and deep partial thickness wounds, in contrast to Biobrane which is used for the most part in more superficial wounds (see above). Although one author (58) observed that TransCyte may not adhere well to deeper burns, he still felt that its use was warranted in those cases due to the delivery of bioactive substances to the wound, and that TransCyte, early in the course of the injury, may serve to “seal the wound”. These deeper burns may prove the niche where the higher cost of TransCyte can be justified.

In cases where an autograft is expected to be required, Integra Bilayer Matrix Wound Dressing may be superior in that it requires only an epidermal autograft or a very thin split-thickness skin graft as opposed to the split-thickness graft required with TransCyte.

Although TransCyte, built on Biobrane, offers many of the characteristics of the ideal wound dressing, and may have added benefits from the delivery of ECM and growth factors to the wound, the downside of high cost and less convenient storage and usage are considerable barriers to its broader adoption.

**Conclusion**

Both Biobrane and TransCyte have a strong body of evidence supporting their use in acute wounds. The most important clinical advantages of both products are prevention of wound dessication, reduction in pain, reduced dressing changes, and, in most reported studies, an acceleration in healing. TransCyte is considerably more expensive than Biobrane and more difficult to store, as it must be stored at -20° to -70° C, and thawed at 37° C prior to use. Its applications must, therefore, be well-considered. TransCyte may be justified in full thickness and deep partial thickness injuries, whereas Biobrane is more appropriate for more superficial wounds.
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55. TransCyte Label.


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