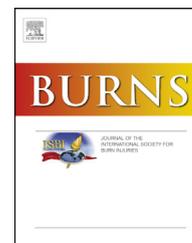


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# The optimal timing of outpatient Biobrane™ application for superficial and mid dermal partial thickness burns: Evidence for the ‘12-hour rule’



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## ABSTRACT

**Background:** Biobrane™ is a skin substitute used for the definitive management of partial thickness burns. No studies have examined the optimal timing of Biobrane™ application in this setting. The purpose of this study was to determine whether there was a clinically significant difference in applying Biobrane to a superficial and mid dermal partial thickness burn within 12h after burn.

**Methods:** From August 2016–February 2017, 29 consecutive superficial and mid dermal partial thickness burn injuries were prospectively treated with Biobrane™ within 12h of the injury. This ‘early Biobrane™’ cohort was compared to a historical cohort of 148 patients who were treated with Biobrane™ for superficial and mid dermal burns after 12h after injury during 2015 to 2016. Multivariate regression analysis was used to determine the difference in time to re-epithelialisation and number of outpatient visits between the two cohorts.

**Results:** In the ‘early Biobrane™’ group, the mean TBSA was  $3.5 \pm 2.7\%$  and the mean time to Biobrane™ application was  $7.1 \pm 2.7$  h after burn injury. The mean time to re-epithelialisation in this group was  $9.1 \pm 3.0$  days, and no patients underwent skin grafting. In the ‘delayed Biobrane™’ group, the mean TBSA was  $2.6 \pm 2.8\%$  and the mean time to Biobrane™ application was  $35.1 \pm 21.4$  h. The mean time to re-epithelialisation was  $14.8 \pm 8.7$  days, with 3 patients undergoing skin grafting. Regression analysis demonstrated a statistically significant 63% reduction in time to re-epithelialisation (95% CI=0.23–0.60;  $P < 0.0001$ ) with early Biobrane™ application.

**Conclusion:** Patients treated with application of Biobrane™ within 12h of superficial and mid dermal partial thickness burns have a statistically significant reduction in healing time when compared to patients treated with standard Biobrane™ practice.

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## 1. Introduction

Biobrane™ is a bilaminar bioengineered skin substitute used frequently in the management of burn injuries. It is composed

of a thin semipermeable flexible silicone membrane bonded to a layer of non-biodegradable nylon matrix which itself is covered with a monomolecular layer of porcine-derived type I collagen. Among its various applications in burns surgery, Biobrane™ has utility in the definitive treatment of superficial

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and mid dermal partial thickness burn wounds. In this setting, Biobrane™ adheres firmly to the dermis of an adequately prepared wound and temporarily performs the functions of lost epidermis until re-epithelialisation occurs. A number of studies of Biobrane™ have demonstrated faster healing, reduced need for grafting, decreased hospital stay, and decreased pain levels when compared to other dressing materials [1–3].

In our Burns Unit, superficial and mid dermal partial thickness burn wounds, when treated with Biobrane™ within 12h of the injury, were subjectively healed quicker, reduced the length of inpatient admission or number of outpatient visits, and decreased the need for skin grafting. Although the literature examining Biobrane™ is extensive, no studies have yet specifically examined the optimal timing of its application when used as definitive treatment of the burn wound.

The purpose of the present study was to determine whether early application (within 12h of the burn injury) of Biobrane™ for superficial and mid dermal partial thickness burn injuries was optimal in terms of clinical outcomes.

## 2. Methods

### 2.1. Study design

Over a 6-month period between August 2016 and February 2017, consecutive adult patients above the age of 18 years referred to the Burns Ambulatory Care Clinic at the Burns Unit, Concord Repatriation General Hospital in Sydney, Australia with superficial and mid dermal partial thickness burn injuries within 12h of the burn injury were recruited.

Twenty-nine such patients were recruited. These patients were all treated in an outpatient setting via oral opioid and inhalational (methoxyflurane) analgesia adjusted to burn size and location. Once deemed comfortable, patients underwent application of Biobrane™ using aseptic technique with sterile drapes. With sponges soaked in a warmed normal saline solution, wounds were debrided of all blistered or loose skin, and the wound surface was gently scrubbed. Biobrane™ was then applied to the wound and secured to normal skin with Hypafix™. No patients underwent general anaesthesia or received hydrosurgical debridement.

The following information was collected for each patient in the ‘early Biobrane™’ group prospectively:

- patient demographics (age, gender)
- smoking status
- total body surface area (TBSA) burned
- burn mechanism
- first aid adequacy
- time to Biobrane application (inh)
- time to re-epithelialisation from date of burn (i.e. when the patient was discharged from our Burns Unit with no requirement for dressings)
- number of outpatient visits
- need for skin grafting

The ‘early Biobrane™’ cohort was then compared to a retrospective historical cohort. All patients with superficial and mid dermal burn injuries treated definitively with the

application of Biobrane™ by our Unit in an outpatient setting more than 12h after burn between 2015 and 2016 were identified using database information from the New South Wales Agency for Clinical Innovation Statewide Burn Injury Service. During this period, patients presenting with superficial and mid dermal burns were treated with Biobrane™ in an identical manner to that described previously. These target time frame of Biobrane application was within 48h of the burn injury. Patients who received Biobrane™ within 12h of the burn injury between 2015 and 2016 were excluded.

The aforementioned database included prospectively collected data. The de-identified data was collected by trained nurses at our Burns Unit and then submitted to the New South Wales Agency for Clinical Innovation Statewide Burn Injury Service. A total of 148 patients were identified via database review. Information collected for each patient by database review was identical to that described earlier.

Superficial and mid dermal burn wounds were defined clinically by the presence of blistering, brisk capillary return, pink and moist dermis, and preserved sensibility. All wound depth assessments were undertaken by the senior author (P.K. M) and occurred at presentation immediately prior to application of Biobrane™. Prior to presentation to our Unit, referring clinicians were instructed to decompress fluid filled blisters but leave blistered skin intact, and to dress all wounds with at least 2 layers of paraffin-impregnated gauze in order to prevent desiccation. Presentation to our Unit followed promptly for patients in the ‘early Biobrane™’ cohort. For patients in the ‘delayed Biobrane™’ cohort, presentation occurred within 48h of the referral.

Adequate first aid was defined as the application of 20min of cool, running tap water up to 3h following the burn injury.

### 2.2. Statistical analysis

Statistical analyses were performed using SAS software (SAS® Version 9.4, [www.sas.com](http://www.sas.com)) and R language, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Baseline characteristics between the ‘early Biobrane™’ and ‘delayed Biobrane™’ were compared using Fisher’s Exact chi-squared tests for categorical variables (gender, burn mechanism, smoking status, adequacy of first aid, and need for grafting) and Wilcoxon rank sum tests for continuous variables (age, TBSA, time to Biobrane™, time to re-epithelialisation, and number of outpatient visits).

Two distinct multivariate regression models were formed to assess relationships between early application of Biobrane™ (independent variable) and 2 dependent (outcome) variables, adjusting for appropriate potential confounders:

1. Time to re-epithelialization (for patients who did not need skin grafting)
2. Number of outpatient visits (for patients who did not need skin grafting)

Associations between adequate first aid and time to re-epithelialisation as well as number of outpatient visits were only conducted among patients that did not undergo skin grafting as both these outcomes were altered by operative intervention.

Model 1 was analysed by Cox regression, adjusting for age, TBSA, adequate first aid, and burn mechanism, and a hazard ratio (with 95% Confidence Interval) was determined. Model 2 used Poisson regression adjusting for the same covariates as Model 1, and the least squares mean (change in outcome) and 95% Confidence Interval were determined.

The temporal relationship between Biobrane™ application and time to re-epithelialisation was further analysed using LOESS regression curve-fitting.

Statistical significance was defined as a P value <0.05 and all statistical tests were two-tailed.

### 2.3. Ethical approval

Institutional ethics approval was obtained for the purposes of this study (reference number 2008/11/113).

Ethical review was by the New South Wales Population & Health Services Research Ethics Committee. This enabled use of all existing and prospectively collected data within the database of the New South Wales Agency for Clinical Innovation Statewide Burn Injury Service for research purposes.

## 3. Results

Table 1 provides a comparison of the 'early Biobrane™' and 'delayed Biobrane™' groups.

Twenty-nine patients were treated with 'early Biobrane™' (within 12h). There were 23 males (79.3%) and 6 females (20.7%). The mean age at presentation was 38.0±14.3 years [mean±SD (standard deviation)] and the mean TBSA was 3.5±2.7%. The mean time to Biobrane™ application was 7.1±2.7h after burn. The mean time to re-epithelialisation in this group was 9.1±3.0 days.

One hundred and forty-eight patients were included in the 'delayed Biobrane™' group. There were 79 males (53.4%) and 69 females (46.6%). The mean age at presentation was 38.4±14.4 years and the mean TBSA was 2.6±2.8%. The mean time

to Biobrane™ application was 35.1±21.4h after burn. The mean time to re-epithelialisation in this group was 14.8±8.7 days.

No patients in the 'early Biobrane™' group underwent split skin grafting and no complications were observed. Three patients in the delayed Biobrane™ group underwent split skin grafting (i.e. failure of Biobrane™) but this difference was not statistically significant (P=0.44).

### 3.1. Regression models

Table 2 demonstrates the findings of multivariate regression analyses.

Patients who underwent early Biobrane™ application had a statistically significant 63% reduction in time to re-epithelialisation (HR=0.37; 95% CI=0.23–0.60; P<0.0001). Early application Biobrane™ was also associated with less number of outpatient visits (effect size –0.29; 95% CI=–0.54 to –0.04; P=0.02).

Fig. 1 shows a LOESS curve of time to re-epithelialisation as a function of time to Biobrane™ application. Optimal re-epithelialisation times were observed when Biobrane™ was applied before 12h (dashed red line, Fig. 1). After this 12h 'cut-off', re-epithelialisation times rose steadily before a relatively stable plateau was seen with increasing time to Biobrane™ application.

## 4. Discussion

This pilot study is the first to provide an evidence base for the optimal timing of Biobrane™ application with respect to superficial and mid dermal partial thickness burn injuries. We found that patients treated with application of Biobrane™ within 12h of the burn had a statistically significant reduction in healing time compared to more delayed treatment with Biobrane™. Re-epithelialisation occurred on average nearly 6 days (63%) faster with Biobrane™ applied within 12h of the burn compared to standard Biobrane™ practice. Benefits were

Table 1 – Comparison of 'early Biobrane™' and 'delayed Biobrane™' cohorts.

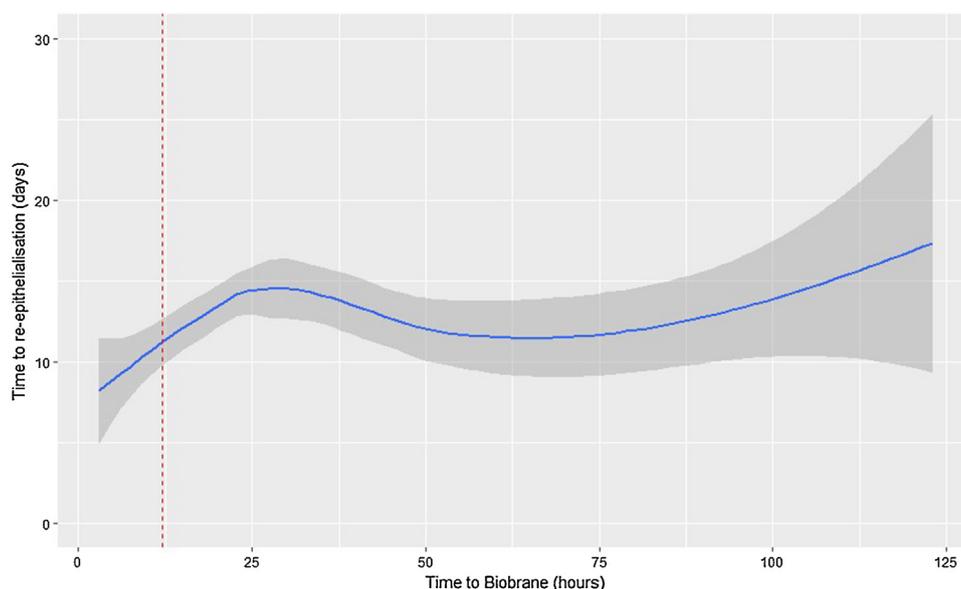
Characteristic	Early Biobrane™ (n=29)	Delayed Biobrane™ (n=148)	p-Value <sup>a</sup>
Sex			<0.001
Male	23 (79.3%)	79 (53.4%)	
Female	6 (20.7%)	69 (46.6%)	
Age	38.0±14.3	38.4±14.4	0.94
TBSA (%)	3.5±2.7	2.6±2.8	0.02
Mechanism			<0.0001
Scald	12 (41.4%)	98 (66.2%)	
Flame	6 (20.7%)	32 (21.6%)	
Flash	11 (37.9%)	6 (4.1%)	
Contact	0 (0.0%)	6 (4.1%)	
Other	0 (0.0%)	6 (4.1%)	
Adequate first aid	20 (69.0%)	105 (70.9%)	0.83
Time to Biobrane™ (hours)	7.1±2.7	35.1±21.4	<0.0001
Time to re-epithelialisation (days; among non-grafted patients)	9.1±3.0	14.8±8.7	<0.0001
Number of outpatient visits (among non-grafted patients)	3.2±2.2	3.5±2.8	<0.0001
Needed skin grafting	0 (0%)	3 (2.0%)	0.44

<sup>a</sup> Pearson's chi-squared for categorical variables and Wilcoxon rank sum for continuous variables.

**Table 2 – Multivariate analyses of clinical outcomes comparing early vs. delayed Biobrane™.**

Outcome	Effect size	95% Confidence interval	p-Value
Time to re-epithelialisation (among non-grafted patients)	HR 0.37	0.23-0.60	<0.0001
Number of outpatient visits (among non-grafted patients)	–0.29	–0.54 to 0.04	0.02

HR, hazard ratio.



**Fig. 1 – LOESS regression curve of relationship between time to Biobrane™ application and time to re-epithelialisation for superficial and mid dermal partial thickness burns with 95% confidence bands (gray shade). Dashed red line corresponds to 12 h to Biobrane™ application. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)**

seen independent of the burn mechanism, body surface area of the burn injury, the patient's age, and the adequacy of first aid. In addition, when time to re-epithelialisation was plotted as a function of time to Biobrane™ application (Fig. 1), maximal benefits with respect to healing time were observed within 12 h (dashed red line). Beyond this '12-hour' point, re-epithelialisation time increased steadily before plateauing, further validating our statistical analysis.

Biobrane™ is not a novel treatment for partial thickness burn wounds. Various studies report the benefits of Biobrane™ in the definitive treatment of a partial thickness burn injury when used within 24 h [2,4,5] or 48 h [1,6,7] from the time of burn injury. No studies, however have specifically examined the optimal timing of Biobrane™ application. In a survey of all burn units in the United Kingdom, 73% of units applied Biobrane™ to injuries occurring within 48 h, and the remaining 27% placed it on older injuries [8]. The results of our study indicate that maximal benefits are seen when Biobrane™ is applied within 12 h of the burn injury. Although we examined superficial and mid dermal burn wounds only, we believe that the '12-hour rule' can be extrapolated to deeper dermal injuries when Biobrane™ is used as a 'trial of life' (provided the wound bed is not desiccated).

Although superficial and mid dermal partial thickness burn injuries generally respond to conservative treatments, these wounds can undergo "secondary deepening" or "spontaneous

conversion" to deeper injuries [9,10]. Burn wound conversion has its origin in Jackson's description of burn injury zones, in which three zones of tissue damage occurred after burn injury [11]. The middle or transitional zone of stasis includes unburned tissue under ischaemic conditions, which may or may not progress to necrosis in 24–48 h. Regression in the zone of stasis is pivotal since conversion often contributes to greater burn surface area and depth, which has multiple local and systemic consequences that increase morbidity [12]. A number of mechanisms may underpin the pathophysiology of burn wound progression including inflammatory mediators, ischaemia, reactive oxygen species, and autophagy [13]. The '12-hour rule' targets these pathogenetic processes, much like early or immediate excision and closure of a deep burn wound, which has been shown to ameliorate inflammatory mediator burden [14,15] and oxidant activity [16]. As these inflammatory cytokines are generated rapidly after a burn injury [17], and since burn progression has been shown to occur within 24 h of the injury [18], application of Biobrane™ within 12 h of the burn injury will obviate the pro-inflammatory cascade, and its local and systemic sequelae.

Sealing the burn wound early with Biobrane™ has additional effects. The harbinger of burn wound infection and sepsis is bacterial colonisation, with source bacteria easily introduced onto the exposed and vulnerable burn surface via both exogenous and endogenous routes [19]. Indeed,

colonisation occurs immediately after burn injury via the endogenous route [20]. Morbidity is increased the longer colonisation persists [21] and is proportional to the size of the skin breach [20]. Wounds are also rendered more vulnerable to colonising pathogens due to local wound factors including the loss of a protective barrier and burn oedema [22]. Debridement of a partial thickness burn within 12h of the injury and immediate application of Biobrane™ therefore presents a unique opportunity to decrease bioburden, maintain the barrier function of the skin, and reduce sequelae of bacterial colonisation. Interestingly, infection rates reported with Biobrane™ application range from 5% to 38% in the literature [23–26] although the term infection is not consistently defined. In our study, no infections occurred in the ‘early Biobrane™’ cohort providing further support for the ‘12-hour rule’.

The result of blunting the local inflammatory response and sealing the burn wound is dermal preservation and possibly ‘reversal’ of wound progression. Rapid re-epithelialisation ensues. This is significant because healing time is strongly linked to ultimate scar formation [27,28]. Thus, a mean re-epithelialisation time of under 10 days for Biobrane™ application within 12h after burn may reduce the rate of hypertrophic scarring. Although this was not specifically examined by our study, future research is being directed at the effect of early Biobrane™ on scarring. Nevertheless, we believe a reduction in healing time as well as a reduction in the number of follow-up visits has obvious economic and psychosocial implications, including decreased health care costs, improved patient satisfaction, and earlier return to function.

Our study adds to the body of evidence for Biobrane™ in the adult population, with most of the available evidence conducted in paediatric patients. Some limitations of our study, however, warrant mention, including the analysis of a heterogeneous patient cohort of both a prospective and retrospective nature. Additionally, burns depths were assessed clinically in this study so utilisation of a burn depth assessment tool such as Laser Doppler imaging may have provided an objective means of comparing depth between the two cohorts. Throughout the period of study, however, the senior author (P.K.M) undertook all depth assessments, thereby minimising bias. Indeed, whilst it is true that burn wounds whose depths are indeterminate clinically are the most challenging [29], this study included only superficial and mid dermal partial thickness burn wounds, which are promptly diagnosed by their pink, moist surface under the cover of blisters, brisk capillary refill within 2s, and preserved sensibility. These individual parameters were all met for each wound before the wound was deemed appropriate for intervention with Biobrane™ and the literature suggests clinical assessment of burn wounds is reliable [30,31]. We believe Laser Doppler imaging adds very little to assessing wounds that are clinically consistent with superficial or mid dermal injuries.

Larger studies are needed to verify the findings of this study, especially as they apply to larger body surface area wounds and/or all partial thickness burn injuries. We believe the ‘12-hour rule’ has applicability to all partial thickness burn wounds that maintain some degree of blistering and are free of desiccation. This requires establishment of clinical pathways

and infrastructure to support this practice, and our Unit now routinely employs the ‘12-hour rule’ for Biobrane™ in the management of partial thickness burns where this is logistically feasible.

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## 5. Conclusion

Our pilot study shows that Biobrane™ applied within 12h of a superficial and mid dermal partial thickness burn is associated with a significantly faster time to re-epithelialisation compared to standard or routine practice. This study is the first in the literature to specifically examine the optimal timing of Biobrane™ application. Likely pathophysiological mechanisms underpinning the ‘12-hour rule’ include immediate wound closure and dermal preservation, blunting of the local inflammatory cascade, prevention of further bacterial colonisation, and possibly reversal of wound conversion. Further study is warranted to examine the effect of the ‘12-hour rule’ for all partial thickness burns.

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## Declarations of interest

None.

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## Ethics

Institutional ethics approval was obtained for the purposes of this study (reference number 2008/11/113).

Ethical review was by the New South Wales Population & Health Services Research Ethics Committee. This enabled use of all existing and prospectively collected data within the database of the New South Wales Agency for Clinical Innovation Statewide Burn Injury Service for research purposes.

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