Pilot Clinical Evaluation of PoreSkin: A Human Acellular Dermal Matrix in Burn Scars

Apichai Angspatt MD*, Tanapron Termwattanaphakdee MD*,
Pornprom Muangman MD***, Tanom Bunaprasert MD**

** Division of Plastic and Reconstructive Surgery, Department of Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*
*** Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*
**** Trauma Division, Department of Surgery, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand*

Background: *An extensive full-thickness wound need a graft, sometime very large. However, donor sites are often limited. Dermal substitutes are among the tissue-engineered products applied to clinical use. PoreSkin, a human acellular dermal matrix (hADM) manufactured by the Faculty of Medicine, Chulalongkorn University, is the first human dermal substitute developed in Thailand.*
Objective: *Assess the safety and ability in achieving durable and definitively cosmetic coverage using PoreSkin.*
Material and Method: *Eleven hypertrophic burn scars were enrolled in the present study. After scar excision, PoreSkin was placed followed by delayed split-thickness skin graft, three weeks later. The primary outcomes were the engraftment rate of the Poreskin and the skin graft. The secondary outcomes included complications and the final cosmetic appearance.*
Results: *The engraftment rate of PoreSkin was 97.7% at day 21. The engraftment rate of autologous sheet skin graft placed over PoreSkin was 91.8%. Regarding the quality of the scar, using the Vancouver scar scale, it shows a statistically significant improvement ($p<0.05$). No major complications or rejection were observed.*
Conclusion: *The performance of PoreSkin as a human acellular dermal matrix (hADM) is comparable to other commercial dermal substitutes in term of engraftment rate, complications, and rejection.*

Keywords: *Burns, Dermal regeneration template, Human acellular dermal matrix, Partial-thickness wound, Wound healing*

J Med Assoc Thai 2017; 100 (4): 441-6
Full text. e-Journal: *http://www.jmatonline.com*

The loss of skin has been one of the most frequent and costly problems in the health care system. An unstable, hypertrophic scars or scar contracture is commonly developed after imperfect wound healing needing to be restored functionally and esthetically. In the past, the treatment of post-burn contracture has been to use skin grafting, flaps, or tissue expansion to reconstruct form and function[1]. The main problem is the lack of sufficient donor site for full-thickness skin grafting and flap in patients with extensive burns. Split-thickness skin grafting is the most reliable and simplest way to treat major burns. Unfortunately, the tissue quality of the split-thickness skin graft sometimes appears incompatible with the original skin and consequently develops contracture[2].

Skin has been the first tissue-engineered organ from the laboratory bench to a patient in 1975, when Rheinwald and Green managed to culture human primary epidermal cell that has physical properties closely resembling to normal skin[3]. In 1981, Burke and Yannas published preliminary clinical results of the use of a bilayer artificial skin (Integra) as a permanent wound coverage[4]. There are substantial evidences that tissue-engineered materials provide benefit to patients such as good healing and appearance closely resembling normal skin[5]. The dermal substitutes serve as a template for dermal repair, faster dermal maturation, improve dermal maturation, improve restoration of dermal organization, improve the scar quality, and reduce skin contraction[5,6].

Most of the currently available skin substitutes use biological materials of allogenic or xenogenic origin. Theoretically, tissue-engineered products must attach well to the wound bed and supported by new vasculature. These products must

Correspondence to:
Angspatt A, Division of Plastic and Reconstructive Surgery Department of Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
Phone: +66-81-4913657
E-mail: aangspatt@hotmail.com

not be rejected by the immune system and be capable of self-repair throughout a patient's life[7]. The development, regulation, manufacture, and marketing make them expensive[8]. The characteristics of ideal wound dressings or biological skin substitutes were first suggested by Pruitt and Levine and have been expanded upon by others in recent years (Table 1)[9]. We developed and clinically tested a human acellular dermal matrix (PoreSkin) that possesses many of these characteristics.

PoreSkin is a bilayer human acellular dermal matrix (hADM) that is a porous wet-sponge collagen and has a thin sheet of semi-permeable silicone membrane coverage (oxygen transmission rate 15.0728 kg m/m^2 hrPa, water vapor transmission rate 0.095$\pm$0.031 kg/m). The collagen is made from an extraction of allograft materials (human cadaveric dermis). The dermal extracts solution is fabricated to have 2 mm-thick membranes, then it has lyophilization. The membrane is a highly interconnected porous structure with average pore size of 150$\pm$29 μm. The chemical composition of PoreSkin is similar to human dermis. Small amount of chondroitin 6-sulfate is added to replace the natural glycosaminoglycan, which is partially lost during the dermal extraction process.

Table 1. Characteristics of the ideal biologic skin substitute

Characteristics
Absence of antigenicity
Tissue compatibility
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
Stably enhance using nonviral vectors

PoreSkin was tested for safety and efficacy evaluation according to international standard (ISO 10993 and US FDA guidance for industry; chronic cutaneous ulcer and burn wound-developing products for treatment). The safety tests were done according to ISO 10993-5 and ISO 10993-6. The ISO 10993-5 cytotoxicity/cytocompatibility was tested and certified for safety by the National Metal and Materials Technology Center (MTEC), Thailand. The ISO 10993-6 was tested using muscle implantation in 24 Wistar rats comparing with Gelfoam at two and four weeks. The local tissue reaction of PoreSkin was similar to Gelfoam. Animal wound model study was done in 16 Guinea pigs according to US FDA guidance for industry; chronic cutaneous ulcer and burn wound-developing products for treatment. The efficacy end points were inhibition of wound contraction and formation of the new collagen in porous cavity of scaffold at the third week. The result has shown that PoreSkin can induce porous new collagen formation pattern with good wound-bed attachment. Contraction study has shown that the wound covered with PoreSkin contracted less than control wound of 40.47% (p<0.0001).

The aim of the present study was to assess the safety and efficacy of PoreSkin in the treatment of burn scar (hypertrophic scar) in human. This was a pilot study. Safety was assessed through observation for any general or local reaction including erythema, infection, fever, and rejection of the graft. Cosmetic appearance and quality of the healed wound were evaluated using Vancouver scar scale.

Material and Method

A prospective, opened label, phase I clinical trial pilot study was conducted at the Division of Plastic and Reconstructive Surgery, King Chulalongkorn Memorial Hospital, Bangkok, Thailand between September 2009 and July 2010. The study was approved by the Ethic Committee (IRB No. 283/52). Eleven hypertrophic burn scar in eight patients were enrolled in the study. All of the hypertrophic burn scar lesions were excised, the defects were measured to collect baseline data, then PoreSkin, a human acellular dermal matrix was implanted in each lesion. At 21-day postsurgery, each wound was assessed for its engraftment and any complications, then the silicone layer was removed and a thin autograft (8 in 1,000 inch) was placed on the neodermis. The wound was again assessed after five days for skin graft engraftment. The quality of the scar were evaluated using Vancouver Scar Scale at three and six months postoperation[10,11].

Study endpoints

The primary outcome measures are the engraftment rate of the PoreSkin and the skin graft. The secondary outcome measures are complications, reaction, and the final cosmetic result. The SPSS software package for window version 14.0 was used for statistical analysis (SPSS, Chicago). Pair t-test analysis was used for difference in Vancouver scar scale pre- and post-operatively. The *p*-value less than 0.05 was considered significant.

Results

Eleven hypertrophic burn scar lesions in eight patients took part in the present study. The demographic data were presented in Table 2. The engraftment rate of PoreSkin is 97.7% at day 21. The area of 2x1 cm at the wound edge in one lesion out of eleven was found not completely grafted by PoreSkin. The engraftment rate of autologous sheet skin graft placed over PoreSkin is 91.8%. Minor skin reaction (erythema) was noticed in one case (Table 3). Using the Vancouver scar scale, the scars were statistically significant improved ($p<0.05$), (Table 4).

Discussion

Successful treatment with an acellular dermal matrix requires low antigenicity, rapid vascularization capability, and stability of the scaffold. Dermal template provides platform for partial-thickness skin graft and cultured keratinocytes. The human acellular dermal matrix provides a thicker and longer dermis compared to those derived from xenogenic dermis. These are better in terms of cell infiltration, angiogenesis, and incorporation.

PoreSkin is a human acellular dermal matrix (hADM) that contains a highly porous structure for skin repair preference. The pore size and pore orientation influence cell behavior. The pore properties such as porosity, pore dimension, and pore volumes are parameters directly related to cell accommodation. Since the diameter of fibroblasts is about 10 μm[12], the microfabricated scaffolds with 100 to 1,000 μm pores were mostly used to orient cells and collagen deposition in engineered tissue scaffold[13]. The collagen dermal replacement layer serves as a matrix for the infiltration

Table 2. Demographic data

Sex/age	%burn	Study side
1) Male/30	Scald 23%	Lt. forearm
2) Female/49	Scald 42%	Rt. forearm
3) Female/49	Scald 42%	Lt. forearm
4) Male/20	Scald 12%	Chest wall
5) Male/52	Flame 5%	Rt. hand
6) Female/50	Scald 42%	Lt. arm
7) Female/50	Scald 42%	Lt. forearm
8) Female/20	Chemical (acid) 14%	Chest wall
9) Male/31	Scald 23%	Lt. forearm
10) Male/31	Scald 23%	Chest wall
11) Male/51	Flame 35%	Abdomen

Table 3. Reaction and percentage of engraftment in PoreSkin and autograft

Erythema	% PoreSkin engraftment day 21	% STSG engraftment day 5
1) No	100	100
2) No	100	100
3) No	100	100
4) Yes day 4	75	50
5) No	100	100
6) No	100	100
7) No	100	100
8) No	100	100
9) No	100	100
10) No	100	100
11) No	100	60
X	97.7	91.8
±SD	7.53	18.34

Table 4. Preporative and postoperative Vancouver scar scale

Patient	Vancouver scar score		
	Preop	Postop 3 m	Postop 6 m
1	6	0	0
2	10	3	2
3	11	9	8
4	10	8	6
5	4	3	0
6	9	2	1
7	9	3	1
8	8	4	2
9	8	1	0
10	11	2	2
11	5	2	1
Mean	8.27	3.36	2.09
p-value		0.000	0.000

of fibroblasts, macrophages, lymphocytes, and capillaries derived from the wound bed. As the healing progresses, an endogenous collagen matrix is deposited by fibroblasts and simultaneously, the dermal layer of the artificial dermis is degraded. Angiogenesis can be induced using dermal substitute products because their dermal fibroblasts produce angiogenesis growth factor[14]. However, the vascularization of dermal substitutes are slower than the autoskin graft[15]. Upon adequate vascularization of the dermal layer and availability of donor autograft tissue, the temporary silicone layer is removed and a thin layer of patial-thickness ski autograft is placed over the 'neodermis'. Cells from the epidermal autograft grow and form a confluent stratum corneum, thereby closing the wound reconstituting a functional dermis and epidermis[13].

The engraftment rate of PoreSkin is 97.7%. The engraftment rate of autologous sheet skin graft placed over PoreSkin is 91.8% which is very much similar to the other dermal matrix commercially available in the market. Total infection rate is 18.2%, which is not much different from the other studies of dermal skin substitute[12,16]. No major complication was found in the present study, which was similar to most of the study using bioengineered skin substitutes[17].

The quality of the scar after surgery was better (Fig. 1). Using the Vancouver scar scale, the scars were statistically significantly improved ($p<0.05$), which was the same result reported from most of the studies[10,18]. Itching was another problem encountered with burn scar but rarely mentioned in the literature. Even after wound maturation, itching still disturbed the patients. In the present study, the itching resolved. This is possibly because the neo-dermis was similar to normal skin, whereas sensory nerve endings were different in scar tissue. This result was similar to the study of Kazutaka Seojima[1] and David Heimbach[4]. They found that itching in the dermal substitute site was significantly decreased.

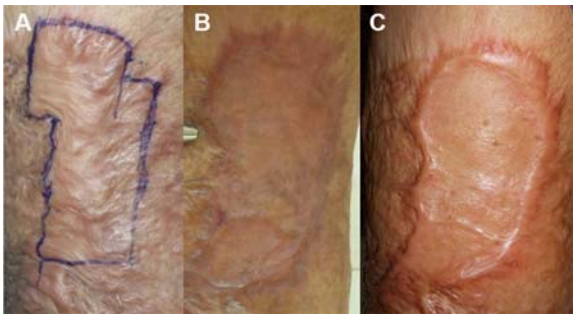

Fig. 1 The appearance of the skin (A) pre-operation (B) 3 month post-operation (C) 6 month post-operation.

The limitation of the present study is the small sample size and short term follow-up. Different types of wound treatment with PoreSkin are required for further investigation.

Conclusion

PoreSkin is a human acellular dermal matrix (hADM) that is composed of a porous wet-sponge collagen covered with a sheet of a semi-permeable silicone membrane. Its engraftment rate, infection rate, and results are not different from the other dermal matrix commercially available in the market. This product is safe and effective as a choice of human acellular dermal matrix.

What is already known on this topic?

Human dermal matrix is known to play an important role in burn patient and other reconstructive procedure.

What this study adds?

PoreSkin, a first and only human dermal matrix developed in Thailand, has been proven to have the same properties as other commercial human dermal matrix in term of benefit and safety. The engraftment rate of PoreSkin is excellent. There are no signs of rejection or complications.

Acknowledgements

We gratefully acknowledge the laboratory of the National Metal and Materials Technology Center (MTEC), Thailand to kindly test the properties of study material, PoreSkin.

Potential conflicts of interest

None.

References

1. Soejima K, Nozaki M, Sasaki K, Takeuchi M, Negishi N. Reconstruction of burn deformity using artificial dermis combined with thin split-skin grafting. Burns 1997; 23: 501-4.
2. Chou TD, Chen SL, Lee TW, Chen SG, Cheng TY, Lee CH, et al. Reconstruction of burn scar of the upper extremities with artificial skin. Plast Reconstr Surg 2001; 108: 378-84.
3. B□ttcher-Haberzeth S, Biedermann T, Reichmann E. Tissue engineering of skin. Burns 2010; 36:

450-60.
4. Heimbach D, Luterman A, Burke J, Cram A, Herndon D, Hunt J, et al. Artificial dermis for major burns. A multi-center randomized clinical trial. Ann Surg 1988; 208: 313-20.
5. van Zuijlen PP, Lamme EN, van Galen MJ, van Marle J, Kreis RW, Middelkoop E. Long-term results of a clinical trial on dermal substitution. A light microscopy and Fourier analysis based evaluation. Burns 2002; 28: 151-60.
6. Ryssel H, Gazyakan E, Germann G, Ohlbauer M. The use of MatriDerm in early excision and simultaneous autologous skin grafting in burns—a pilot study. Burns 2008; 34: 93-7.
7. MacNeil S. Progress and opportunities for tissue-engineered skin. Nature 2007; 445: 874-80.
8. Li A, Dearman BL, Crompton KE, Moore TG, Greenwood JE. Evaluation of a novel biodegradable polymer for the generation of a dermal matrix. J Burn Care Res 2009; 30: 717-28.
9. Pruitt BA Jr, Levine NS. Characteristics and uses of biologic dressings and skin substitutes. Arch Surg 1984; 119: 312-22.
10. Fearmonti R, Bond J, Erdmann D, Levinson H. A review of scar scales and scar measuring devices. Eplasty 2010; 10: e43.
11. Baryza MJ, Baryza GA. The Vancouver Scar Scale: an administration tool and its interrater reliability. J Burn Care Rehabil 1995; 16: 535-8.
12. Venugopal J, Ramakrishna S. Biocompatible nanofiber matrices for the engineering of a dermal substitute for skin regeneration. Tissue Eng 2005; 11: 847-54.
13. Freed LE, Guilak F, Guo XE, Gray ML, Tranquillo R, Holmes JW, et al. Advanced tools for tissue engineering: scaffolds, bioreactors, and signaling. Tissue Eng 2006; 12: 3285-305.
14. Griffith LG, Naughton G. Tissue engineering—current challenges and expanding opportunities. Science 2002; 295: 1009-14.
15. Sahota PS, Burn JL, Heaton M, Freedlander E, Suvarna SK, Brown NJ, et al. Development of a reconstructed human skin model for angiogenesis. Wound Repair Regen 2003; 11: 275-84.
16. Heimbach DM, Warden GD, Luterman A, Jordan MH, Ozobia N, Ryan CM, et al. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. J Burn Care Rehabil 2003; 24: 42-8.
17. Pham C, Greenwood J, Cleland H, Woodruff P, Maddern G. Bioengineered skin substitutes for the management of burns: a systematic review. Burns 2007; 33: 946-57.
18. Nguyen DQ, Potokar TS, Price P. An objective long-term evaluation of Integra (a dermal skin substitute) and split thickness skin grafts, in acute burns and reconstructive surgery. Burns 2010; 36: 23-8.

การศึกษานำร่องทางคลินิกของผิวหนังเทียม PoreSkin ในแผลเป็นที่เกิดจากบาดแผลไหม้

อภิชัย อังสพัทธ์, ธนพร เติมวัฒนาภักดี, พรพรหม เมืองแมน, ถนอม บรรณประเสริฐ

ภูมิหลัง: *การรักษาบาดแผลไหม้ที่มีขนาดใหญ่มักจะต้องทำการรักษาด้วยการปลูกถ่ายผิวหนัง และบ่อยครั้งที่ประสบปัญหาไม่มีผิวหนังปกติเพียงพอที่จะทำการปลูกถ่ายผิวหนังเทียมที่ได้จากกระบวนการทางวิทยาศาสตร์เป็นวิธีการหนึ่งที่สามารถแก้ไขปัญหาดังกล่าวแต่ผิวหนังเทียมเชิงพาณิชย์ที่มีจำหน่ายในปัจจุบันแม้จะมีประสิทธิภาพสูงแต่มีราคาสูงมาก PoreSkin เป็นผิวหนังเทียม (human acellular dermal matrix) ที่พัฒนาขึ้นเป็นครั้งแรกในประเทศไทยโดยคณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

วัตถุประสงค์: *การศึกษานี้เป็นการศึกษานำร่อง โดยมีจุดประสงค์เพื่อจะทดสอบความปลอดภัยและคุณสมบัติของผิวหนังเทียมที่ผลิตได้ทั้งในส่วนของความทนทานและความสวยงาม*

วัสดุและวิธีการ: *ผู้ทำการศึกษาได้ทำการรักษาแผลเป็นนูน (hypertrophic scar) 11 แผลเป็นผู้ป่วยทุกคนหลังจากได้รับการผ่าตัดแผลเป็นออกจะได้รับการปลูกถ่ายผิวหนังเทียมที่ผลิตขึ้น หลังจากนั้นสามอาทิตย์ก็จะได้รับการปลูกถ่ายผิวหนังจริง (split-thickness skin graft) การวัดผลหลักจะวัดจากอัตราการสำเร็จของการปลูกถ่ายผิวหนังเทียมและอัตราการสำเร็จของการปลูกถ่ายผิวหนังจริง การวัดผลรองจะวัดจากอาการแทรกซ้อนปฏิกิริยาต่อผิวหนังเทียมและความสวยงาม เมื่อบาดแผลหายดีแล้ว*

ผลการศึกษา: *อัตราการสำเร็จของการปลูกผิวหนังเทียมเท่ากับ 97.7% ในสัปดาห์ที่สามและอัตราการการสำเร็จของการปลูกถ่ายผิวหนังจริงเท่ากับ 91.8% หลังจากบาดแผลหายดีแล้วคุณภาพของแผลเป็นที่วัดด้วย Vancouver scar scale ดีขึ้นกว่าเดิมอย่างมีนัยสำคัญทางสถิติและในศึกษานี้ไม่พบอาการแทรกซ้อนหรือการไม่ยอมรับเนื้อเยื่อ*

สรุป: *โดยสรุปผลของการศึกษาผิวหนังเทียม PoreSkin พบว่ามีคุณสมบัติใกล้เคียงผิวหนังเทียมเชิงพาณิชย์ในต่างประเทศ ทั้งในแง่ของอัตราการสำเร็จของการปลูกถ่ายและอาการแทรกซ้อน*