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Porcine xenografts vs. (cryopreserved) allografts in the management of partial thickness burns: Is there a clinical difference?☆

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ABSTRACT

Porcine xenografts and cryopreserved allografts are used for the management of partial thickness burns and both biological materials have strong advocates with regard to clinical performance, the possibility of disease transfer from donor to recipient and other clinical aspects. A literature analysis was performed in an attempt to investigate whether true (statistically significant) differences exist on clinical performance and on other determinants for use.

Comparing the results of this study with a similar, previously published study performed on possible differences amongst different types of allograft in the management of partial thickness burns, both allografts and porcine xenograft seem to perform equally well clinically with regard to healing related outcomes. In addition, the risk of disease transfer, in real life, was shown to be minimal. Consequently, clinical aspects being equal, other aspects such as price and availability should be used to decide which material to use for the management of partial thickness burns.

1. Introduction

Biological dressings, xenografts as well as allografts, have been used for the management of burns for long while, with the first documented application going back several centuries [1]. Porcine skin is available as preserved skin (particularly with glutaraldehyde [2]), and as decellularised matrices [3] while it has also been combined with silver in an attempt to lower colonisation levels [4]. Skin allografts are available in different forms as well, with glycerol immersion and cryonic techniques most commonly used for preservation.

Both allografts and xenografts are used as dressings for partial thickness burns, as a temporary dressing in excised, non-grafted burns [5,6] and as dressings for chronic lesions and non-thermal skin loss injuries [7–13]. Allografts are also used as cover dressings in excised and grafted full thickness burns [14] while xenografts are sometimes used on skin graft donor sites [15].

All biologic dressings are known to provide a series of properties that are beneficial for the patient and the wound [16]. When applied to partial-thickness wounds, all seem to increase the speed of healing when compared with traditional dressings [17–19].

Xenografts and (particularly) cryopreserved allografts (CPA) also have distinct differences and both types of biological dressings have strong advocates, predominantly with regard to viability and its (perceived) role in supporting wound healing, and the (potential for) disease transfer (Table 1).

A literature search was undertaken, aimed at analysing whether these differences are relevant for the clinic with

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Table 1 – Theoretical (perceived) differences between xenografts and cryopreserved allografts.

	Xenografts	Cryopreserved allograft	Literature evidence
Disease transfer	Zoonotic diseases Porcine Endogenous Retroviruses *Clostridium difficile*	Human viruses HIV CMV Hepatitis	Actual incidence of disease transmission through grafts is extremely low [32]
Viability of graft	Cells are dead	Viability depends on type of preservation agent [63] but possible	No clinical impact in rat study [22] or human comparative study with dead vs. viable allograft [20]
Secondary loss of grafts through contamination	Irrelevant	Significant [30,31]	Literature evidence [30,31]
Availability	Supply "unlimited"	Supply determined by availability donors and preservation infrastructure [39,40]	
Dressing size and format	Whole sheet, meshed, on a role	Whole sheet and meshed, relatively small vs. xenograft	

regard to the management of partial thickness burns. Other aspects that might play a role in deciding on a certain type of graft, such as availability and pricing, also were investigated.

2. Search methods and search results

The databases of Pubmed, Medline, Google and the search engine of the Endnote X5 programme (Thompson Reuters, Carlsbad, CA, USA) were searched, focussing primarily on partial thickness burns, porcine skin, porcine derived matrix, preservation methods, as well as on related topics such as bacteriology (including disease transfer), cost, and outcomes, particularly healing, pain and long term results.

Articles on dressings made of the submucosa of the porcine small intestine were excluded (since it is a different type of tissue) as were articles on pig skin as a donor site dressing since allografts are not used for the treatment of donor sites. Search results were analysed and compared with previously published, similar data on cadaver skin [20].

3. Preservation methods, risks of disease transfer

Porcine skin is most commonly preserved with glutaraldehyde: its protein crosslinking properties have a biocidal and preservative effect on tissues, making xenografts more durable and safe [21] while killing the cells in the graft. (The lack of) viability does not seem to have a clinical impact: in a test with a rat recipient wound model, viable (fresh) vs. preserved porcine skin did not show any difference in clinical performance [22]. A study on clinical performance of allografts, preserved using different methods, showed similar results (no difference in reepithelialization between dead and viable cells) [20].

Depending on the preservation technique used, zoonotic infections from pigskin (above all porcine endogenous retroviruses (PERV) and *Clostridium difficile*) are a potential threat but, to date, no evidence of pig-human PERV transfer has been found [23] and *C. difficile* infections, while fairly common in burn patients, have not been shown to be of zoonotic origin [24].

Transfer of human diseases via allografts, particularly infections with viruses such as HIV, CMV and hepatitis, is a risk [25,26] and transmission of cytomegalovirus and HIV has been described with CPA [26–29]. Donors also have a fairly high contamination rate, leading to the need to secondarily discard a significant percentage of allografts [30,31] which has an impact on overall cost. However, the actual incidence of disease transmission through grafts is shown to be low, both in humans [32] as well as in animal experiments [23,33,34].

To reach the necessary level of safety with CPA extensive donor culturing is necessary, while more modern genomic techniques contribute to a high level of safety [35,36]. Quality control is paramount and donor screening, whether the donor is a human or a different species, is strictly regulated by governments [37,38]. Generally speaking, it is easier to control animal donors than human ones, since animals are raised in a better controlled environment.

4. Availability and costs

Skin allograft availability is limited by the number of donors, which is restricted [39] and unpredictable over time as well [40]. Cadaver skin also requires a designated and expensive infrastructure which has to include harvesting teams which have to be available at odd times, extensive culturing facilities, and a skin bank for preservation and storage. These are among the reasons why many regions in the world do have limited or no immediate access to cadaver skin [41]. Financial, cultural and religious influences play a prominent role in the (non) acceptance or availability of human organs for transplantation purposes [42] while in other cultures primarily religious influences play a role in not-accepting animals for transplant purposes [43].

Xenografts are available mainly from commercial suppliers and supply is sufficient and well controlled. Since the source is controlled stock, quality control is easier and less extensive (and, thus less expensive) than for allografts.

Both human allograft skin and xenografts are available as whole sheet and meshed products but xenografts are available in more, different (i.e. on a role) and larger formats. Direct

Table 2 – Comparison of the price of different dressings, indicated for the management of partial thickness burn (amended from [64]).

Product type	Size (cm)	Cost per unit	Cost per cm^2	Shelf life
Acellular human dermal matrix	2 × 4	$ 272	$ 34.00	24 months (1 °C–10 °C
	4 × 7	$ 336	$ 12.00	
Porcine xenograft, glutaraldehyde preserved	8 × 10	$ 25	$ 0.31	18 months (room temperature)
Cryopreserved xenograft	Many different sizes	$0.15–$0.71	2 years [65] [a]	
Acellular human dermal matrix	2 × 4	$ 216	$ 27.00	36 months (room temperature)
	3 × 7	$ 576	$ 27.42	
Bovine xenograft (collagen)	5 × 7.5	$ 11	$ 0.29	36 months (room temperature)
Skin allograft	Many different sizes	$ 0.92 [66]–$ 5.00	±2 years	

Note: Some prices are estimates only since they depend on the manufacturer/provider and/or size and/or country. For skin allografts, prices also depend on preservation technique (glycerol vs. cryopreservation).

[a] Human to murine models show good clinical performance after five years of cryopreservation [67].

price comparisons between the two types of grafts in a clinical setting have not been published, nor are comparative cost-effectiveness studies available. However, because of the economies of scale, sourcing of the donor, the reduced need for serological and genomic testing of a donor animal and lower cost of storage, particularly for products that do not have to be kept frozen, it is highly likely that porcine xenografts are significantly cheaper per unit as well as in use than CPA and human allograft derived products. Shelf life of biological materials depends on the type of preservation but, for most dressing types, is at least 18 months. Table 2 shows a series of more or less similar products, all indicated for the management of partial thickness burns, and the associated estimated prices.

5. Clinical studies (Table 3)

Relatively few studies on clinical results of porcine skin in burn care have been published and in only two studies xenografts are compared directly to allografts, although healing (reepithelialisation) was not a study objective for either study [44,45]. Two xenograft studies were published in Chinese medical journals, with only the abstracts in English [46,47].

Bacterial clearing of granulating wounds was shown to be similar for allografts and xenografts in a study with 16 patients [44]. In a second study in the same indication the author concludes that although allografts performed somewhat better, ''in the absence of available cadaver allografts, sheet porcine xenograft is a satisfactory substitute for use on granulating wounds to diminish evaporative water loss, while amnion and meshed porcine are less effective'' [45].

Davis et al., in a descriptive article on several types of lesions stated that ''xenografts provide an inexpensive method to facilitate wound care, promote healing, serve as an effective repair option for a variety of surgical defects, are easy to use and often more cost-effective than regular dressings''. The authors recommend that xenografts be used to predict autograft survival and state that these grafts provide for inexpensive wound care, with the cost of a frozen heterograft often being less than the expected home bandage and wound care costs'' [16].

Chiu et al. confirm that xenografts and allografts provide pain reduction and a level of antibacterial protection. They state that, since porcine skin is easier to obtain than allograft, it is their standard dressing for partial-thickness burns'' [39]. Leon-Villapalos confirms the role of, and preference for, porcine skin in burn care, particularly for facial burns [5].

El-Khatib et al. retrospectively compared Biobrane (Smith and Nephew, Hull, United Kingdom) with glutaraldehyde preserved porcine skin in excised burns ($N = 26$ for each group) and reported that both materials reduced pain, decreased evaporative water and heat loss, and limited bacterial growth while promoting the development of granulation tissue [48].

5.1. *Partial thickness burn studies in humans*

A number of studies on partial thickness burns and porcine skin was found: in some of the studies porcine skin was the primary treatment modality while in others porcine skin was combined with other interventions.

A prospective, non-comparative study described results of lyophilised porcine skin application (after excision, if indicated) treatment of 97 patients suffering from, mainly, deep partial thickness, excised burns. The authors looked at the number of dressing changes between the day of excision and hospital discharge (1.51 ± 1.60), use of analgesics during dressing change (not needed in 22.9% of all patients) and the development of granulation tissue underneath the dressing (results not specified) and concluded that the lyophilised porcine matrix could be recommended for use of partial thickness burns [49].

The same authors in a study comparing lyophilised porcine skin to 1% silver sulfadiazine (SSD) in partial-thickness burns conclude that porcine skin is superior in terms of pain control, degree of wound infection, used wound dressings and length of hospital stay [19].

Bromberg, in a study with 19 burn patients, reported porcine xenograft to be a suitable replacement of allografts [50] in terms of the length of time of use and adherence. In a separate study, early application of porcine grafts (covered with Sulfamylon (UDL Laboratories, Rockford, IL) impregnated gauze) was shown to reduce sepsis and to hasten eschar separation in a study of 150 patients with partial and full thickness burns [51].

In a prospective study on partial skin loss (mostly due to thermal injury), porcine skin (13 patients) was found to lead to faster healing than paraffin gauze ($p < 0.001$), provided better

Table 3 – Human trials with porcine full skin and porcine skin derivatives in burns.

Primary author Journal, year of publication	Indication Primary study objective(s)	Type of study Type of porcine product. Comparative material (if any)	Number of patients xenograft/comparator	Main results/conclusion
Bromberg [50] *Minnesota Medicine*, 1965	Partial thickness burns Reepithelialization	Prospective, non-comparative Porcine skin	19	Xenograft suitable replacement for allograft
Rappaport [51] *American Journal of Surgery*, 1970	Partial and full thickness burns General healing criteria	Prospective, non-comparative Porcine skin, covered with Sulfamylon	150	Xenograft reduces sepsis, supports separation of eschar
Chatterjee [17] *Current Medical Research and Opinion*, 1978	Partial thickness skin loss in limbs, mainly burns Healing	Prospective, comparative Porcine skin Paraffin gauze	13/15	Xenograft: significantly faster healing ($p < 0.001$), better reduction of pain, lower rate of infection and sickness absence Xenograft approximately 2/3 less expensive than paraffin gauze
Salisbury [45] *Annals of Plastic Surgery*, 1980	Granulating wounds Evaporative loss from burn dressing	Prospective, comparative Frozen cadaver allograft, fresh amniotic membrane, fresh xenograft (sheet and meshed).	28 wounds 10 patients	In absence of available cadaver allografts, sheet porcine xenograft satisfactory substitute to diminish evaporative loss
Salisbury [44] *Plastic Reconst. Surg.*, 1980	Granulating wounds Bacterial clearing effects (quantitative cultures)	Prospective, comparative Sheet and meshed porcine grafts, amnion membrane, sheet cadaver skin	16 patients, 192 lesions: Sheet porcine grafts: $N = 49$ Meshed porcine graft: $N = 48$ Amnion: $N = 48$ Sheet cadaver skin: $N = 47$	No statistical difference. Fresh porcine skin preferred for second- and third-degree burns because of cost and ease of use
Healy [53] *Burns*, 1989	Partial thickness burns Time to healing Pain Level of contamination	Prospective, comparative Porcine glutaraldehyde xenograft Paraffin gauze	16/16	No significant differences with regard to time to healing, need for surgery, bacterial colonisation, surgical treatment, number of dressing changes, analgesic requirements
Feng [47] *Chinese Journal of Surgery*, 2002 (*only abstract in English*)	Deep partial thickness burns Healing	Retrospective, non-comparative Porcine acellular dermal matrix after excision	128	
Feng [46] *Academic Journal of the First Medical College of PLA*, 2006 (*only abstract in English*)	Deep partial-thickness burns Speed of healing, overall quality of healing	Prospective, comparative Porcine acellular dermal matrix vs. (unspecified) exposure therapy	67/10	''Satisfactory results''. Porcine acellular dermal matrix may promote reepithelialisation
Feng [56] *Burns*, 2006	Deep partial thickness burns Long term scar formation	Retrospective, comparative Porcine acellular dermal matrix vs. povidone-iodine ointment exposure	20/20	Faster healing (2 wks. vs. 4 wks) and significantly better scarring in porcine group: 3 months post burn: $p = 0.0012$ 6 months post burn: $p = 0.0009$
El-Khatib [48] *Annals of Burns and Fire Disasters*, 2007	Excised, non-grafted, deep dermal and full thickness burns. Promotion granulation tissue	Retrospective, Comparative Glutaraldehyde preserved porcine vs. Biobrane	26/26	Both materials reduce pain, evaporative water loss, heat loss. Both limited bacterial growth and promote granulation tissue

Table 3 (*Continued*)

Primary author Journal, year of publication	Indication Primary study objective(s)	Type of study Type of porcine product. Comparative material (if any)	Number of patients xenograft/comparator	Main results/conclusion
Hosseini [49] *Burns*, 2007	Excision of deep partial thickness burns, coverage with xenograft Frequency of dressings, hospital stay, duration of analgesia use, wound infection, formation of granulation and scars at burns site	Prospective, non-comparative Lyophilised acellular porcine matrix	97	Xenoderm reduces frequency of dressings, hospital stay, pain and analgesic: use of xenoderm in the treatment of second degree burns recommended
Hosseini [19] *Asian Journal of Surgery/Asian Surgical Association*, 2007	Deep partial thickness burns Frequency of dressings, hospital stay, analgesia use, wound infection, formation of granulation and scars	Prospective, comparative Lyophilised acellular porcine matrix vs. SSD	39/37	All parameters reduced vs. SSD: ''the use of this porcine matrix in the treatment of second degree burns is recommended''
Bukovcan [54] *Acta chirurgicae plasticae*, 2010	Partial thickness burns Time to healing	Retrospective non- comparative Porcine skin	109	78 patients (71%) healed within 14 days with a mean time of 9.6 days. Skin xenografts showed good adherence wound surfaces, decreased amount of exudate, reduced pain, low risk of hypertrophic scarring
Duteille [52] *Burns*, 2012	Intermediate partial thickness facial burns Long term follow up (3,6,12 months) on quality of healing	Prospective, non-comparative. Glutaraldehyde preserved porcine skin after hydrosurgery	20	Mean healing time: 13.4 days. Months mean scar satisfaction score: 7.84 (10 meaning no scar)
Review articles				
Leon-Villapalos [5] *Burns*, 2008	Facial burns Review article		Porcine skin has an important role to play in the management of facial burns	
Davis *Dermatologic Surgery*, 2000	General review article		Porcine xenografts promote granulation, particularly also in relatively avascular areas. Inexpensive method to facilitate wound care. Easy to use, often more cost-effective than regular dressings. Prediction of autograft survival	
Chiu [39] *Clinics in Dermatology*, 2005	General review article		Biologic dressings adhere without need for additional fixation. Antibacterial action is function of adherence. Protect against physical trauma, provide heat and moisture retention. Allografts perhaps more effective but supply severely restricted. Porcine skin standard dressing for partial-thickness burns. Also role in providing temporary coverage of full-thickness defects and for debriding burns/ulcers	

pain reduction and was estimated to be 1/3 of the cost of paraffin gauze for a comparable size burn [17].

Duteille and colleagues treated 20 patients with partial thickness facial burns with early hydrosurgery, followed by the application of glutaraldehyde preserved porcine skin, with a short term and long term (12 months after discharge) follow up. The authors reported a mean initial healing time of 13.4 days with normal healing in 17 patients, and stated that xenografts may augment facial healing while reducing the number of dressings and lessening patient discomfort [52].

In a prospective randomised trial of 32 patients with partial skin thickness burns (face and hands excluded) glutaraldehyde preserved porcine skin was compared to a paraffin gauze dressing. No statistically significant differences with regard to bacterial colonisation rate, need for surgical treatment, time for spontaneous healing, analgesic requirements and frequency of dressing changes were found between the two groups [53].

Bukovcan and colleagues retrospectively analysed 109 patients with partial-thickness scald burns, treated with porcine xenografts, and reported healing within 14 days of 71% of all patients healed within 14 days (mean: 9.6 days) and an overall mean healing time for all patients of 15.1 days. The authors report good adherence on the wound surfaces, a decreased amount of exudate and reduced pain.'' In addition, the risk of hypertrophic scar formation was lower when wound healing was achieved within 14 days [54].

Feng et al. compared the long term scar quality in 20 patients with deep partial thickness burns, treated with a porcine acellular dermal matrix or with three-times-daily debridement and application of povidone-iodine ointment. All patients treated with the matrix healed within 2 weeks versus up to four weeks with the iodine treatment. At 12 months assessment the Vancouver scar scale [55] showed significantly lower scores for the porcine matrix treated wound ($p = 0.009$) [56].

The same authors also published two articles in Chinese journals about the use of porcine skin, with only an English abstract (and limited information). A retrospective review of 128 cases shows ''successful treatment with satisfactory clinical results'' in superficial and deep partial thickness burns, treated with a 0.1% benzalkonium bromide wash, tangential excision (deep partial thickness burns) and subsequent application of porcine acellular dermal matrix [47]. A second article presents the results of 67 patients with large (total body surface area: 50–90%) deep partial thickness burns, treated by a single application of porcine acellular dermal matrix. Results were compared to (unspecified) exposure treatment (10 patients) with regard to healing time (matrix: 12.2 days on average, exposure 27.4 days on average) and long term follow up ''showed a much better scar quality in the porcine group'' [46].

6. Discussion

All biological dressings share a number of properties: they protect the wound from fluid, protein and heat loss and from physical trauma, while providing pain relief and relatively fast (compared to more conventional materials) healing and reepithelialisation. Long term results (with regard to scarring and scar quality) are better than with conventional materials as well, among other reasons because these materials increase wound healing [57]. Both xenograft and cadaver skin have strong advocates and the purpose of this article was to analyse if, in clinical use, real differences exist.

The literature on porcine skin and its derivatives in clinical burn care is surprisingly limited, particularly in light of the fact that this type of xenograft for this indication has been in use for a long time. In addition, the quality of many of the trials described in the articles found in our search is not of a high standard and poorly standardised with regard to outcomes and how they are measure.

However, a number of outcomes, favourable for porcine skin versus a number of different dressings is consistently mentioned and include reduction of pain [17,19,48,54], antimicrobial properties [39,44,48,54], reduction of chances of sepsis, and good quality long term results [46,47,52,54,56]. The reepithelialisation time of porcine skin treated partial thickness burns is in line with those reported for skin allograft as previously reported in this journal [20]: Khoo [14] and Rose [58] found average healing times of 19 days with glycerolised allografts, Eldad reported 76% reepithelialisation within 21 days [59] with cryopreserved allografts and Vloemans showed that (only) 39.6% of all partial thickness burns did not reach complete reepithelialisation when threated with glycerol allografts on PBD 14, thus requiring secondary grafting [60].

Xenografts and allografts seem to have some differences with regard to the period during which the dressing stays adherent to the wound (where allografts are superior) and the possibility of the patient developing a reaction (to the porcine protein in xenografts). However, both aspects are less important for (smaller) partial thickness burns and could not be substantiated by a literature search.

Xenografts were also shown to be relatively cheap, even when compared to paraffin gauze [17] and other traditional materials [16]. Although a direct cost comparison between cryopreserved allografts and xenografts in the management of partial thickness burns is not available, it is highly likely that the use of xenografts contributes significantly to lowering the cost of care: while clinical performance is similar, procurement, preservation and storage of xenografts are all significantly lower than those of allografts. In addition, the potential risk of disease transfer from donor to recipient is lower with xenografts.

7. Limitations

Given the long history of using allograft and xenografts in burn care, the number of (comparative) clinical trials is surprisingly small and for the two studies with the largest number of patients treated with porcine xenografts only an abstract is available in English. The lack of standardisation in trials with (biological) dressings is a major limitation of this, and any, literature review [61]. In the articles on porcine materials referenced here many crucial aspects, such as depth of a burn, healing and reepithelialisation were ill defined. The methodology of many of the trials was poor and study objectives were diverse and inconsistent. Generally, the level of evidence was

not very high by the standards of the Oxford Centre for Evidence Based Medicine [62]: in fact, many of the studies found in this literature search were observational or anecdotal in nature.

Consequently, the lack of scientific evidence is a major limitation of this type of literature review but it is nearly intrinsic in analysing dressing performance in burn care. However, better comparisons are not possible, simply because they have not been performed and/or published. At the same time, although most studies are anecdotal, their results are consistent and therefore may indicate trends.

8. Conclusion

In spite of the strong beliefs and perceptions amongst clinicians, no evidence was found showing that xenograft, their derivatives, or allografts perform better clinically in the management of partial thickness burns. All these materials provide rapid reepithelialisation, pain relief, protection of the wound and, generally, good long term results.

Therefore, clinical outcomes being equal, the decision of choosing one type of biological dressing over another has to be based on other aspects, such as biological safety, (off the shelf) availability, and price. If these arguments are taken into account, porcine xenografts may very well be the better choice since they provide safety and efficacy for a low price.

Conflict of interest

The author, Michel Hermans, is a paid consultant for Mölnlycke Health Care, Gothenburg, Sweden.

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