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THE USE OF AMNIOTIC MEMBRANE FOR WOUND HEALING IN BURN INJURIES

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ABSTRACT

Introduction: Burn injuries are associated with significant mortality and morbidity around the world. The care of burn wounds requires a great amount of medical resources, therefore it is important to find a wound dressing that accelerates wound healing and is readily available.
Methods: Literature search from online databases using relevant keywords about the usage of amniotic membranes in burn patients.
Results: Research has shown that it contains antimicrobial properties that could be of great benefit in burn patients and is compatible to use in developing countries because it is readily available, easy to obtain and sterilize, able to cover wounds of large size, protects the wound from excessive water and electrolyte loss, reduces pain intensity, requires fewer dressing changes and is also more cost effective than conventional dressings.
Conclusion: Amniotic membrane is a biological dressing that can be useful in the treatment of burn wounds. Further research should be conducted to investigate and understand the mechanisms of amniotic membrane for burn and wound care.

Highlights:

1. An organic bandage that can be helpful in the treatment of burn wounds is amniotic membrane.
2. The mechanisms of amniotic membrane for the treatment of burns and wounds should be investigated and understood in more detail.

INTRODUCTION

Burns are the fourth most common type of injury, following motor vehicle accidents, falls, and interpersonal violence[1]. The incidence of burn injuries is higher in developing countries. In Indonesia, it is estimated that around 195,000 deaths occur annually from burn injuries[2]. According to the World Health Organization (WHO), there are high rates of mortality, with approximately 1.3 burn patients per 100,000 people in Southeast Asia[3]. The patient's survival is highly dependent on the speed and effectiveness of wound healing. After the second week following a burn, it is believed that bacterial sepsis of the wounds is the leading cause of mortality in burn patients[4].

It is crucial to choose a simple, inexpensive, and widely available dressing because wound care involves a substantial amount of medical resources[5]. Using amniotic membrane as a biological dressing to temporarily close a wound has been documented in the last century. The amnion is a thin tissue that forms the fetal membrane's innermost layer. In addition, current research indicates it is one of the most effective biological dressings for burn wounds[6]. This study will provide an overview of the literature and background of the usage of amniotic membrane in burn patients. We will also discuss its properties of preventing infections, relieving pain, and how it accelerates wound healing.

Methods

The study searched by Pubmed and Scopus with keywords “amniotic membrane” and “wounds”. Articles were obtained from different databases. The selection was carried out carefully based on title and abstract, research study categories, and full-text.

Results

History of Amnion Membrane use in Wound

The amniotic membrane is the deepest layer of the placenta and can be detached with ease by blunt dissection. Histologically, the amniotic membrane consists of three primary layers: epithelium, basement membrane, and an avascular stroma[7]. The membrane is avascular, tough, and transparent. In 1910, Davis was the first to utilize amniotic membrane for skin transplantation, which dates back over a century[8]. The benefits stated at the time were pain reduction, reduced risk of infection, and healing support. Douglas did not discover the potential of amniotic membrane as a temporary burn wound dressing until 1952[9].

Burn wounds, chronic ulcers, intra-oral and genital reconstruction, hip arthroplasty, and corneal abnormalities are now treated globally with human amniotic membrane, a comparatively cost-effective and efficacious dressing. It can be acquired through cesarean sections under sterile conditions. It can be stored momentarily or preserved using glycerol, silver nitrate, antibiotic solution, or liquid nitrogen[10]. The development of amniotic membrane applications expanded knowledge of its features and traits that could be utilized. In recent years, preservation techniques have also improved and become more widely available.

How The Amnion Membrane Works

Multiple components in human amniotic membrane contribute to its anti-scarring, anti-inflammatory, anti-bacterial, and analgesic activities. Multiple cytokines, growth factors, metalloproteinases, and anti-inflammatory proteins are known to be exclusive to the amniotic membrane. Wound healing is

Table 1. Summary of Literature Review

Authors	Title	Year	Results
Mohammadi et al.[5]	Human amniotic membrane dressing: An excellent method for outpatient management of burn wounds	2008	In a randomized controlled clinical experiment with a single-blind, amniotic membrane was associated with faster wound healing, fewer needs for skin grafts, and less discomfort compared to the control group.
Branski et al.[11]	Amnion in the treatment of pediatric partial-thickness facial burns	2007	Significantly fewer patients treated with amnion required dressing changes.
Koob et al.[13]	Biological properties of dehydrated human amnion/chorion composite graft: Implications for chronic wound healing	2013	Using enzyme-linked immunosorbent assays (ELISA), human amnion allografts were examined for the presence of growth factors, including TGF-, EGF, PLGF, bFGF, GCSF, and cytokines including IL-4, IL-6, IL-8, and IL-10.
Haugh et al.[20]	Amnion membrane in diabetic foot wounds: A meta-analysis	2017	A meta-analysis of ulcers of the extremities treated with amnion membrane showed a significantly greater success rate than conventional dressing during a 6-week period.
Mao et al.[21]	Anti-microbial peptides secreted from human cryopreserved viable amniotic membrane contribute to its anti-bacterial activity	2017	The anti-microbial activity of amniotic membrane against common pathogens in chronic wounds, mediated by anti-microbial peptides (AMPs) including human beta-defensins (HBDs), was demonstrated.

greatly influenced by the inflammatory process, and the amniotic membrane can play a vital role in this regard.

Amnion can be used to facilitate the treatment of burn injuries by improving wound healing, creating a moist environment, reducing pain intensity, minimizing scar formation, preventing water and electrolyte disturbances, and minimizing the risk of infection. Human amnion is typically applied to burns of the second degree that have already been debrided. It is applied to the wound until it has fully healed, which depends on the severity of the wound and exudate. Full-thickness burns may also be covered temporarily with amniotic membrane in preparation for more permanent wound closure. It has also been demonstrated that the amniotic membrane promotes the migration and adherence of epithelial cells in burn wounds[5,11].

The amniotic membrane has also been shown to promote migration and adhesion of epithelial cells in burn wounds. Some growth factors that contribute to this are epidermal growth factor (EGF), placental growth factor (PLGF), transforming growth factor α (TGF-α), basic fibroblast growth factor (bFGF), and granulocyte colony-stimulating factor (GCSF). These growth factors also promote angiogenesis, the development of new blood vessels from the capillaries that already exist[12]. It also contains anti-inflammatory cytokines, including IL-4, IL-6, IL-8, IL-10, and tissue inhibitors of metalloproteinase (TIMP) 1, 2, and 5[13].

Current Evidence Supporting The Use

The anti-inflammatory effects of amniotic membrane have been extensively discussed. The stromal matrix of the amniotic membrane has shown an ability to inhibit the expression of potent pro-inflammatory cytokines such as IL-1 and IL-1[14]. The inflammatory cytokine IL-1 mediates the extravasation of phagocytes and lymphocytes to the site of inflammation and plays a crucial role in the inflammatory

Table 2. Summary of The Benefits of Amniotic Membrane for Burn Wound Healing

Effect	Detail
Anti-inflammatory	It contains properties that suppress inflammatory cytokines, such as IL- 1α, IL-1β, TNF-α, IL-64, IL-6, IL-8, and IL-10.
Anti-microbial	It provides mechanical protection against infectious organisms and contains transferrin, bactricidin, β-lysin, lysozymes, and immunoglobulins.
The acceleration of re-epithelialization	It stimulates epithelial cell migration and adhesion in burn wounds. Epidermal growth factor (EGF), placental growth factor (PLGF), transforming growth factor (TGF-), basic fibroblast growth factor (bFGF), and granulocyte colony-stimulating factor are among the growth factors that contribute to this (GCSF).

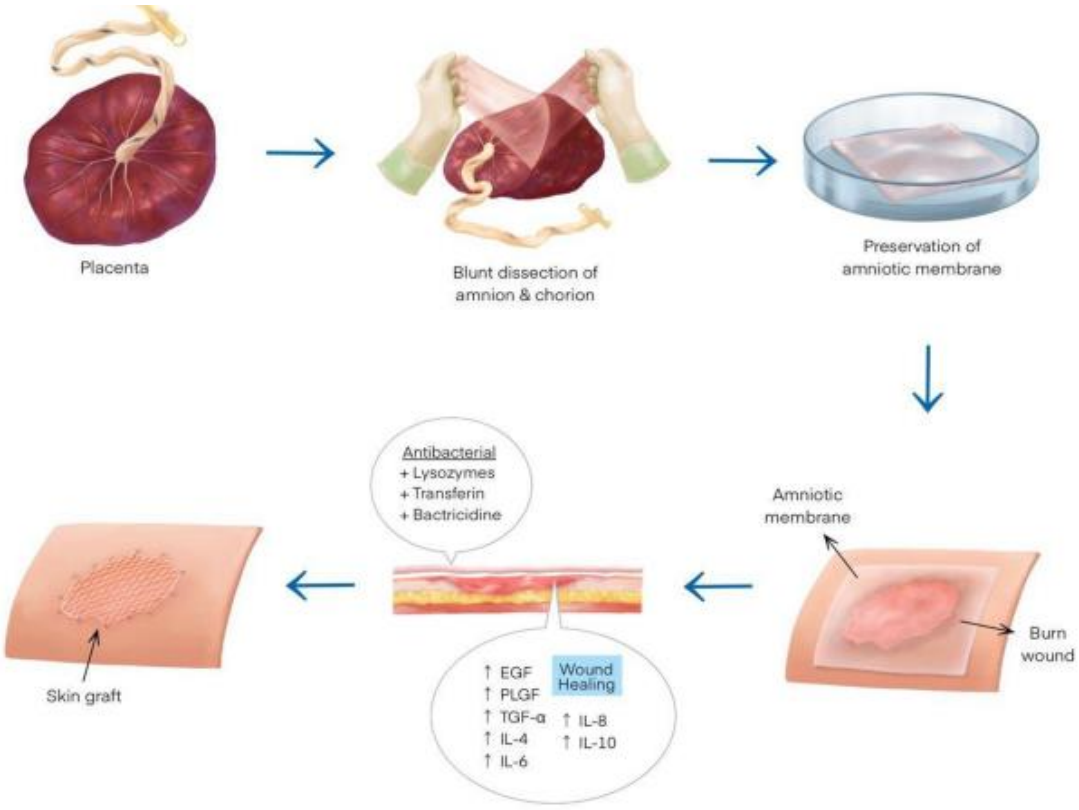

Figure 1. The Process of Obtaining Amniotic Membrane from a Placenta

cascade. Amniotic membrane contains IL-1 receptor agonists (IL- 1RA) that can inhibit immune cell migration. It also contains IL-10, which is able to inhibit important inflammatory factors such as TNF-, IL-6, and IL-8, which promote neutrophil and granulocyte migration to the site of inflammation[15]. Amniotic membrane has the ability to downregulate these pro-inflammatory cellular components. It also contains hyaluronic acids in large quantities, which act as a ligand for CD44 that helps the adhesion of lymphocytes[16].

Human amniotic membranes have anti-microbial properties, making them an optimal temporary biological dressing for burn injuries. It is able to provide mechanical protection against infectious organisms and

also contains transferrin, bactricidin, β-lysin, lysozymes, and immunoglobulins[17,18]. These molecules were shown to possess anti-bacterial effects against bacteria tha are often seen in burn patients, such as groups B and A *Streptococcus, enterococcus faecalis, E. coli, Staphylococcus saprophyticus, Lactobacillus, P. aeruginosa, and Acinetobacter*[19,20]. Amniotic membrane tested in infected excised granulating burn wounds have also been reported to decrease the number of bacteria. To increase its anti-microbial properties, a technique using impregnation of silver nitrate can be used. Silver nitrate impregnation is performed by placing the amniotic membrane in light-proof bottles for two hours in a solution of 0.5% silver nitrate. Comparing silver-impregnated amniotic membrane to uncoated amniotic membrane, a randomized in vitro study revealed a significant reduction in bacteria when treated with silver-impregnated amniotic membrane[21].

In addition to its anti-inflammatory and anti-bacterial properties, amniotic membrane promotes wound healing by stimulating the migration of keratinocytes, which results in re-epithelialization of the wound[22]. By activating c-Jun, a crucial transcription factor for the progression of re-epithelialization, the amniotic membrane initiates a complex signaling network of events. This has been demonstrated by in vitro wound healing studies. C-Jun is an indispensable component of activator protein-1 (AP-1), an early response transcription factor involved in cell proliferation, differentiation, migration, apoptosis, inflammatory responses, and tumorigenesis. c-Jun is essential for the formation and organization of epidermal cells during wound healing[23]. Amniotic membrane also includes Type IV and Type VII collagen, fibronectic, and lamilins 1 and 5, which stimulate epithelial cell proliferation and adhesion[24].

DISCUSSION

In developing countries with a large incidence of burns, treatment should remain efficient and cost-effective. The risk of infection in burn wounds is high as burn patients tend to have longer stays in the hospital. The nature of the burn wounds and the immune compromise effects of burns need intensive diagnostic and therapeutic procedures[25].

Amniotic membranes as dressings for burn wounds are compatible in developing countries because it is readily available, easy to obtain and sterilize, and more cost-effective than conventional dressings. The other benefits include the ability to cover large-size wounds, protect wounds from excessive water and electrolyte loss, reduce pain intensity, and require less dressing changes[25,26]. In research comparing the cost analysis of amniotic membrane grafts to other biocompatible skin replacements, it was determined that amniotic membrane grafts are much less expensive than other biocompatible skin substitutes[28]. One study revealed that although items containing amniotic membrane had a higher initial cost, the patients who were treated with these items had much reduced costs at the conclusion of their therapy for chronic diabetic foot ulcers. This study revealed that 92% of patients with diabetic foot ulcers saw healing at six weeks, whereas only 8% did so with regular care, thereby justifying the high initial cost of therapy[28].

Concerns with the usage of amnion membrane center around the difficulties of screening the material for viral infections and contamination. The danger of disease transmission must be weighed against the

therapeutic advantages and the donor's known traits[29,30]. Amniotic membrane that has been preserved or used fresh have both been found to function well for wound care. Ideally, serologic testing should be done in the case of a maternal donor for the amniotic membrane. With fresh amniotic membrane, the time of procurement until the transplantation is short. With preserved amniotic membrane, there is more flexibility in the time of usage[31,32]. Preserving amniotic membrane would necessitate the use of a refrigerator, making it problematic in locations with limited resources. Additionally, amniotic membrane has quick decomposition, weak mechanical character- istics, and impractical shapes.

Over the last century, the medical application of amniotic membrane has progressed from a sheet for topical administration to the skin to more sophisticated forms such as micronized dehydrated membrane, amniotic cytokine extract, and solubilized powder injections for regeneration[32,33]. Many of its positive applications as a natural biocompatible material are not yet well recognized. Future developments that could be of high benefit would be to investigate how amniotic membrane could be optimized in order to facilitate its applications. This could be by researching how amniotic membrane could be used in combination with other materials and properties and incorporating technologies such as 3D printing, nanotechnology, and tissue engineering. The advancement of technology in medicine has helped and will continue to improve wound care using amniotic membrane in various forms such as suspension, gel, and sponge[34,35].

CONCLUSION

Burns are complicated injuries that can result in substantial morbidity and death. Infection slow wound healing, scarring, and discomfort are the obstacles that burn care physicians must overcome. Burn wounds can be treated using amniotic membrane as a biological bandage. In developing countries, the benefits, procurement feasibilities, and use of amniotic membrane are advantageous. Even though amniotic membrane has been utilized for wound treatment since the previous century, new studies have demonstrated its benefits. To examine and comprehend the mechanism of amniotic membrane for burn and wound treatment, further research is required.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

All authors contributed equally in writing the report on the results of this study, from the stage of proposal preparation, data collection, analysis, and presentation of the final report.

REFERENCES

1. Peck MD. Epidemiology of burns throughout the world. Part I: Distribution and risk factors. Burns. 2011;37(7):1087-1100.
2. Wardhana A, et al. The epidemiology of burns in Indonesia's national referral

burn center from 2013 to 2015. Burns Open. 2017 Oct 1;1(2):67-73.
3. World Health Organization. Injuries and Violence Prevention Department. The injury chart book: a graphical overview of the global burden of injuries. Geneva: Dept. of Injuries and Violence Prevention,Noncommunicable Diseases and Mental Health Cluster, World Health Organization; 2002. Available at http://apps.who.int/iris/bitstream/10665/42566/1/924156220X.pdf.
4. Ghalambor AA, et al. The amniotic membrane: a suitable biological dressing to prevent infection in thermal burns. Med J Islamic Acad Sci. 2000 January 1;13(3):115-8.
5. Mohammadi A, et al. Human Amniotic Membrane Dressing: an Excellent Method for Outpatient Management of Burn Wounds. Iranian Journal of Medical Sciences, 2009; 34(1): 61-64.
6. Mohammadi AA, Mohammadi MK. How Does Human Amniotic Membrane Help Major Burn Patients Who Need Skin Grafting: New Experiences. In: Spear M, editor. Skin Grafts - Indications, Applications and Current Research [Internet]. London: IntechOpen; 2011 [cited 2022 May 19]. Available from: https://www.intechopen.com/chapters/18941. doi: 10.5772/23107
7. Cirman T, et al. Amniotic membrane properties and current practice of amniotic membrane use in ophthalmology in Slovenia. Cell Tissue Bank,2014.15:177–192
8. Davis JW. Skin transplantation with a review of 550 cases at the Johns Hopkins Hospital. Johns Hopkins Med J. 1910;15:307
9. Douglas B: Homografts of fetal membranes as a covering for large wounds especially those from burns: An experimental and clinical study. J Tenn Med Assoc 45:230-235, 1952.
10. Halim AS, et al. Biologic and synthetic skin substitutes: An overview. Indian J Plast Surg. 2010 Sep;43(Suppl):S23-8.
11. Branski LK, et al. Amnion in them treatment of pediatric partial-thickness facial burns. Burns. 2008;34(3):393-399.
12. Rezazadeh D, et al. Autologous amniotic membrane: An accelerator of wound healing for prevention of surgical site infections following Cesarean delivery. Med Hypotheses 2020 Apr;137:109532.
13. Koob TJ, et al. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. Int Wound J. 2013;10(5):493-500.
14. Solomon A, et al.(2001) Suppression of interleukin 1 alpha and interleukin 1 beta in human limbal epithelial cells cultured on the amniotic membrane stromal matrix. Br J Ophthalmol 85: 444-449.
15. Malhotra C, Jain AK. Human amniotic membrane transplantation: Different modalities of its use in ophthalmology. World J Transplant. 2014 June 24;4(2): 111-21.
16. Tseng SC, et al. How does amniotic membrane work? Ocul Surf 2004;2(3):177–87.
17. Talmi YP, et al. Antibacterial properties of human amniotic membranes. Placenta. 1991 May-Jun;12(3):285-8.
18. Sangwan VS, et al. Amniotic membrane transplantation: A review of current indications in the management of ophthalmic disorders. Indian J Ophthalmol. 2007;55:251–60.
19. Haberal M, et al. The use of silver nitrate incorporat amniotic membrane as a temporary dressing.Burns Incl Therm Inj 1987;13:159–63.

20. Haugh AM, et al. Amnion Membrane in Diabetic Foot Wounds: A Meta-analysis. Plast Reconstr Surg Glob Open. 2017 25;5(4):e1302.
21. Mao Y, et al. Antimicrobial Peptides Secreted From Human Cryopreserved Viable Amniotic Membrane Contribute to its Anti-bacterial Activity. Sci Rep. 2017 Oct 20;7(1):13722.
22. Jay RM, Huish JP, Wray JH. Amniotic membrane in clinical medicine: History, current status, and future use. Mooradian DL, editor. In Woodhead Publishing Series in Biomaterials. Extracellular Matrix-derived Implants in Clinical Medicine. Woodhead Publishing. 2016.(151-176)
23. Ruiz-Cañada C,et al. Chronic Wound Healing by Amniotic Membrane: TGF-α and EGF Signaling Modulation in Re-epithelialization. Front Bioeng Biotechnol. 2021 July 6;9:689328.
24. Mahandaru D, Wardhana A. Nosocomial infection in burn unit of Cipto Mangunkusumo Hospital, Jakarta. Jurnal Plastik Rekonstruksi. 2012;1(3).
25. Zelen CM, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomized, controlled, multi-centre comparative study examining clinical efficacy and cost. Int Wound J. 2016 Apr;13(2):272-82.
26. Gutiérrez-Moreno S, et al. Cost-benefit analysis of amniotic membrane transplantation for venous ulcers of the legs that are refractory to conventional treatment. Actas Dermosifiliogr. 2011,102(4):284-8.
27. Ramakrishnan KM, Jayaraman V. Management of partial-thickness burn wounds by amniotic membrane: a cost-effective treatment in developing countries. Burns. 1997;23 Suppl 1:S33-S36.
28. Jay RM, et al. Amniotic membrane in clinical medicine: History, current status, and future use. Mooradian DL, editor. In Woodhead Publishing Series in Biomaterials. Extracellular Matrix-derived Implants in Clinical Medicine. Woodhead Publishing. 2016; 151-176.
29. Hadjiiski O, Anatassov N. Amniotic membranes for temporary burn coverage. Annals of Burns and Fire Disasters. 1996.
30. Add PJ, e al. Amniotic membrane grafts, "fresh" or frozen? A clinical and in vitro comparison. Br J Ophthalmol. 2001;85(8):905-7.
31. Sangwan VS, et al. Amniotic membrane transplantation, Indian Journal of Ophthalmology:2007; 55(4): 251-60.
32. Tseng SC, et al. How does amniotic membrane work? Ocul Surf 2004;2(3): 177–87.
33. Yue, C., Guo, Z., Luo, Y., Yuan, J., Wan, X., & Mo, Z. (2020). c-Jun Overexpression Accelerates Wound Healing in Diabetic Rats by Human Umbilical Cord-Derived Mesenchymal Stem Cells. Stem cells international, 2020, 7430968.
34. Lee SH, Tseng SC. Amniotic membrane transplantation for persistent epithelial defects with ulceration. Am J Ophthalmol. 1997;123(3):303-12.
35. Elkhenany H, El-Derby A, Abd Elkodous M et al. Applications of the amniotic membrane in tissue engineering and regeneration: the hundred-year challenge. Stem Cell Res Ther 13, 8 (2022).