The Role of the Bovine Amniotic Membrane in Accelerating of Wound Epithelization A Systematic Review and Meta-Analysis

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The Role of the Bovine Amniotic Membrane in Accelerating of Wound Epithelization: A Systematic Review and Meta-analysis

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ABSTRACT

Modern dressings promise a smoother and less visible scar than typical wound management. The bovine amniotic membrane, one of the amniotic membranes that is often to be used in wound management known to be safe and effective in accelerating wound healing. However, no robust data of its effect in accelerating wound healing is available. The aim of this systematic-review and meta-analysis was to provide robust data on the role of bovine amniotic membrane on wound epithelization process. The searches of the eligible studies were conducted in two databases (Medline and PubMed). Data on authors, year of publication, location, type of wound dressing, and the outcomes were collected from each eligible study based on PRISMA guideline. Five studies from the systematic review, included human and non-human wounds, were included in the meta-analysis and all of them used freeze-dried bovine amniotic membrane. Individual study found indicated that freeze-dried bovine amniotic membrane could accelerate epithelialization in wound healing. However, meta-analysis suggested that there was no difference between administration of freeze-dried bovine amniotic membrane and the use of other dressing in term of epithelialization process on wound healing (summary of effect was 69.52and 95% confidence interval (95%CI) from -61 to 200). In conclusion, there areno adequate data and therefore there is no strong evidence from human and non-human wounds to suggest that bovine amniotic membrane accelerates the wound epithelization faster than other types of dressing.

Keywords: Wound healing, bovine amniotic membrane, epithelialization

Introduction

Wound healing is critical in wound management since it is associated with discomfort of the patients. Prolonged wound healing will prolong the treatment period and also leave scars. The main components in the wound healing process are connective tissue, collagen, blood vessels, and epithelium.[1] After an injury, the body will activate cytokines including insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and transforming growth factor beta (TGF-β) which later promote neutrophil chemotaxis and activate macrophages, mast cells, endothelial cells, and fibroblasts.[2-5]

The amniotic membrane provides a promising source of non-invasive mesenchymal stem cells. One of the amniotic membranes that is often used is the bovine amniotic membrane (BAM), derived from the bovine placenta, which could be used as a safe and effective wound dressing.[6] The thickness of BAM is15 mm and this similar to human amnion membrane (HAM) which is 10 mm. Histologically, similar to HAM, BAM consists of a single layer of the cuboidal epithelial cells.[6] Therefore, if BAM could be used instead of the HAM, mass production can be achieved. In addition, other issues such as availability of donors, risk of infection transmission, and ethical issue could be minimized.[7]

A previous study compared the use of the BAM and HAM, and found that both were effective in the treatment of split-thickness skin graft donors.[7]Previous studies also found that the BAMcould release various growth factors.[8-10]Amnion membrane has several roles

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in wound healing including anti-adhesive that reduces inflammation, neovascularization, and fibrosis.[8-10] In veterinary practice, amnion membrane has been applied for ocular surface reconstruction in dogs and horses due to its ability to promote re-epithelialization, reduce fibrosis, and modulate angiogenesis. The amnion sheet as a biological dressing has various active substances such as angiogenic factors which plays a role in the formation of wound granulation tissue and three types of growth factors, EGF, keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF).[5, 6] BAM contains several growth factors that could reduce the regulation of proteolytic enzymes that are important in collagen biodegradation in wound healing. However, robust evidence of the role of BAM in accelerating wound healing is lacking. This systematic-review and meta-analysis sought to provide the data on the role of BAM in accelerating of wound epithelization.

Methods

Asystematic review was conducted to evaluate the role of BAM to accelerate epithelialization in wound healing as of September 2020. The literature searches were carried out in a comprehensive manner according to Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines.[11] The searches were conducted in two databases: Medline and PubMed. The searches were limited to period of 2005-2020. The keywords used were “bovine amniotic membrane” OR “BAM” AND “epithelialization” OR “wound healing”. All reviews, commentaries, editorials, case reports, and case series were excluded. Only articles written in English were included in this study.

The potential studieswere selected based on inclusion criteria: (1) the study assessed the relationship between the BAM and wound healing in animals or humans; (2) the study compared the treatment group with the control group; and (3) the study had sufficient data to be analyzed, such as the effect size with an interval ratio (showing the mean and standard deviation values).The information of the first author, year of publication, location, type of study, and outcomes were collected from each eligible study.

The assessment of heterogeneity was evaluated using I^2 statisticwith a random effect model and the results obtained were presented in the form of a forest plot. Furthermore, the publication bias test was carried out by identifying the funnel plot; if the results are not symmetrical, it could be concluded that there is publication bias. All analyses were conducted using the Stata 16 software.

Results

The searches on both PubMed and Medline databases yielded 39 articles. Further assessment on titles, abstracts, and full text of each articleresulted in five articles that match the inclusion criteria. All five of the articles were included into the meta-analysis. The characteristics of the included articles in the meta-analysis are presented in **Table 1**. In all five studies, bovine freeze-dried amniotic membrane (Amnisite-BA™) was used on the wound area between 8 mm and 30 mm diameters, andall of these studies aimed to evaluate the speed of epithelialization of the wound. The meta-analysis was then conducted to compare the time of epithelialization of the wound between BAM-treated and control group.

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Table 1. The characteristics of studies included in the meta-analysis

Author (year)	Wound area	Type of intervention	Method of application	Intervention group	Control group
Choi et al., 2007[12]	8mm diameter of the Shih-tzu dog's cornea	Freeze-dried BAM (Amnisite-Ba)	Application	Freeze-dried BAM (Amnisite-Ba)	Irrigation with normal saline and ofloxacin ed
Park et al., 2008[8]	30 mm diameter in skin of Yorkshire pigs	Freeze-dried BAM (Amnisite-Ba)	Application	Freeze-dried BAM (Amnisite-Ba)	Polyurethane foam dressing (Allevyns; Smith, UK)
Kim et al., 2009[13]	8 mm diameter on the Shih-tzu dog's cornea	Freeze-dried BAM (Amnisite-Ba)	Application	Freeze-dried BAM (Amnisite-Ba)	Irrigation with normal saline ofloxacin ed
Kang et al., 2013[10]	8 mm diameter on the ears of the New Zealand rabbit	Freeze-dried BAM (Amnisite-Ba)	Injection	*Solution of freeze-Dried bovine amniotic membrane*	Duoderm dressing
Min et al., 2014[9]	Multiple post ablation laser therapy in human skin	Freeze-dried BAM (Amnisite-Ba)	Application	Freeze-dried BAM (Amnisite-Ba)	Duoderm dressing

Based on I^2 analysis results, a random effect test was used. Based on the forest plot table (**Figure 1**), a summary effect value was 69.51 with 95% confidence interval (95%CI) ranged between -61 to 200. This suggests that there was no difference in epithelialization time between the BAM-treatment group and the control group. The publication bias was tested using a funnel plot (**Figure 2**) and the results suggested that all five articles were asymmetrical distributed. This suggests there was a potential for publication bias.

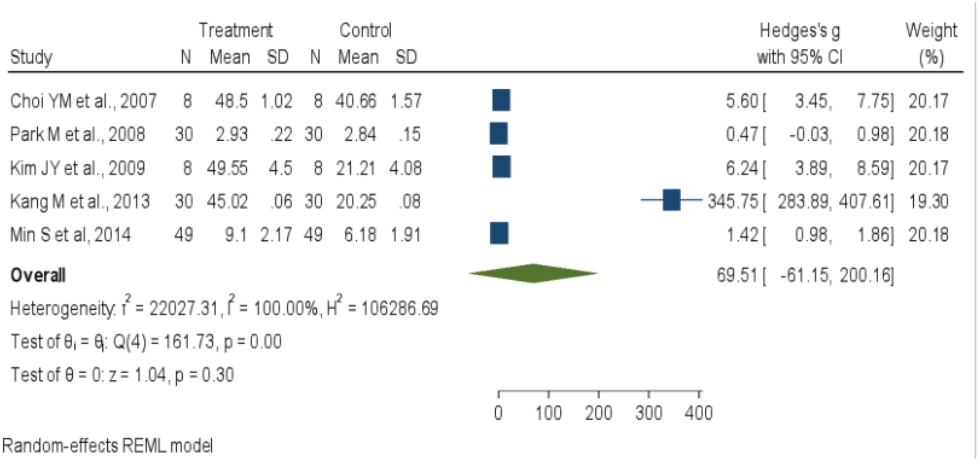

Figure 1. Forest plot showing the comparation of epithelialization time between bovine freeze-dried amniotic membrane (Amnisite-BA™) and control group.

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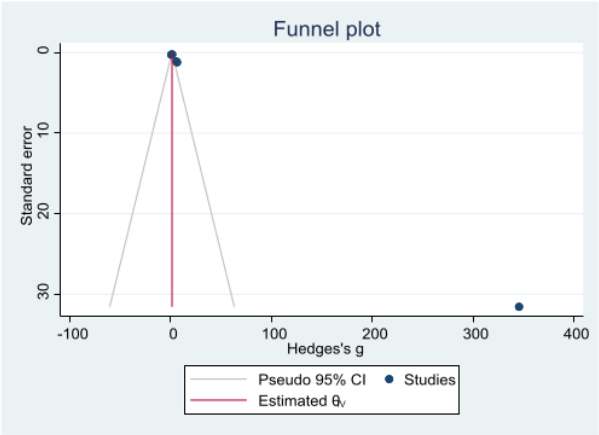

Figure 2. Funnel plot of the study

Discussion

The use of BAM as a source of the amniotic membrane was first tried by Johnson in 1937. Then a study conducted by Rao and Chandrasekharam in 1981 suggested that BAM was safe and had the same effectiveness as a biological wound dressing.[14]In addition, BAM exhibited good wound healing effects, proper fibroblast infiltration, lower bacterial infection, and increased protection against bacterial penetration.[8] This is because BAM acts as a source of non-invasive mesenchymal stem cells and contains several growth factors that could down-regulate proteolytic enzymes, where these proteolytic enzymes play an important role in collagen biodegradation.

A study to evaluate the acceleration of epithelial healing in dog corneas found that BAM could promote epithelial cell growth, strengthen the adhesion of epithelial cells, prevent the apoptosis and therefore it could accelerate the epithelialization in healing wounds.[13] A study on dog corneas also suggested that BAM promoted the epithelial cell growth and strengthened the adhesion of epithelial cells and prevent apoptosis.[12]In rabbits, BAM treatment associated with good epidermis and collagen without signs of infection compared to the group without BAM.[10]In human, a study found that BAM administration after laser ablation therapy also accelerated the time of wound epithelialization compared hydrocolloid dressings.[9]The fibroblast and EGF levels among those treated with BAM was also higher compared to the hydrocolloid dressing group and a significant anti-inflammatory effect was also observed in BAM group.[9]

However, meta-analysis of five available studies suggested that BAM did not increase the time of wound epithelialization compared to control group. There are some explanations of this finding. The number of study and the number of samples was relatively small. In addition, most of the studies were conducted in non-human and only one study assessed the effect in humans. Therefore, more studies are required to validate this finding. In addition, we found the publication bias among five studies using a funnel plot that might due to some factors.

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Conclusion

Our systematic review found that there are no adequate studies assessing the role of BAM on acceleration of wound epithelialization in humans. Mixing both human and non-human cases, our meta-analysis suggests that there is no statistical different of the epithelializationtime between the BAM-treated and non-BAM-treatedwound.

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