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Review

Is allograft skin, the gold-standard for burn skin substitute? A systematic literature review and meta-analysis

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Summary *Background:* Allograft skin (AS) transplantation has been considered to be the gold standard for replacing tissue damage, following burns. However, increasingly new biosynthetic skin substitutes are being developed as alternatives. The objective of this systematic review is to compare AS with other skin substitutes, which have been used in the treatment of burns.
Methods: Randomized clinical trial (RCT) and nonrandomized clinical trial (NRCT) studies comparing AS to any other skin substitute in the treatment of burns were extracted from PubMed/Medline, Scopus, EMBASE, and Web of Science. For the risk of bias analysis, the Cochrane bias risk handbook was used for RCT studies and ROBINS-1 was used for NRCT studies. Outcomes such as healing, self-grafting, scar appearance, and mortality were evaluated.
Results: Twelve RCT and six NRCT were selected, with most of the methodologies presenting a high risk of bias. Based on the outcomes of the studies, it was not possible to detect any advantages for using AS, as opposed to other skin substitutes. In the meta-analysis, only two outcomes could be evaluated: healing and graft take percentage; however, no significant differences were observed between the groups.
Conclusion: Because of the poor quality of the primary studies, it was not possible to identify differences in the results that compared the use of AS with other substitutes in the treatment

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of patients with burns. These results support the fact that surgeons primarily base the choice of skin substitute on clinical experience and cost, at least when treating burns.

Contents

Introduction

Extensive burns provoke critical alterations in the homeostatic processes of the human body and result in high rates of morbidity and mortality.[1] In the initial stage of trauma, the destruction of cutaneous tissue leads to the release of a series of chemical mediators, which cause an intense systemic inflammatory response, with increased capillary permeability and hypovolemic shock.[2] Following clinical stabilization, a hypermetabolic phase begins, in which the absence of a skin barrier makes the individual more susceptible to water loss, as well as bacterial invasion and infection.[3] This is a continuous cycle that ceases only following the debridement and definitive coverage of the lesions with autografts.[4] However, patients with large extensions of total body surface area (TBSA) do not have an adequate amount of skin donor areas, for autogenous grafting, making it difficult to cover all of the wounds.

Under these circumstances, skin substitutes are of fundamental importance for therapeutic success and can increase patient survival.[5] This heterogeneous group of wound care products provide temporary or definitive coverage[6] and are classified depending on whether their origin is biological (allograft skin (AS),[7] porcine skin,[8] and amniotic membrane[9,10]), synthetic (hydrocolloids[11] and hydrogels[12]), or biosynthetic (Integra®[13], Apligraf®[14], and Dermagraft®[15]).

For a skin substitute to be considered ideal, it must have characteristics such as water loss prevention, wide availability, biodegradability, support cellular adhesion, infection resistance, presence of epidermal and dermal components, low antigenicity, high shear strength, easy storage, long shelf life, and good cost-benefit.[16] Currently, no substitute available for clinical use meets all of these criteria, but many authors consider AS the gold standard for burn treatment.[5,17-21]

Girdner performed the first AS transplantation in 1881, but the dissemination of its use took place after the formation of tissue banks, which facilitate the collection, processing, storing, and distribution of allografts and follow strict criteria to ensure safety to the recipients[22] In general, allografts function as a biological dressing that stimulates the re-epithelialization of partial-thickness burns and prepares the wound bed for autografts of full-thickness burns.[23] These skin substitutes can also reduce pain, provide good adherence to the wound bed, reduce microbial load, stimulate vascularization, improve thermoregulation, and can deliver persistent dermal elements for dermal restoration.[23]

In a transversal study,[24] 500 professionals, who specialize in treating large burns, were invited to respond, by e-mail, about the importance of using skin substitutes with patients suffering from burns that cover a large TBSA and their preferences of material for clinical use. A total of 111

specialists, from 36 countries, replied to the questionnaire. Interestingly, 81% of the participants considered skin substitutes essential for the treatment of patients with extensive lesions (i.e., > 60% TBSA), 87% expressed that there was no ideal substitute, but about half (51%) of those surveyed used allografts preferentially.

With AS being considered the gold standard among skin substitutes, ongoing research and development has generated new techniques for the decellularization of human and animal tissues and cultivation of human cells on support matrices and has identified and characterized novel biocompatible chemical substances and biomaterials for treating burn victims.[16] While many of these products appear promising, it is not known whether or not they are capable of generating clinical results similar or superior to those obtained with AS.

Taking into consideration the concepts of evidence-based medicine, the present study aimed to perform a systematic literature review and meta-analysis on studies that compared AS to other skin substitutes or therapies, in the treatment of burn patients. To draw comparisons, clinical trial outcomes such as healing, graft take percentage, scar appearance, and mortality were analyzed.

Method

This systematic review sought to determine how other skin substitutes compare with AS in the treatment of burns, and a meta-analysis was employed to summarize the results of these studies. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[25] was utilized, as a checklist, to control the content produced during the review process.

Search strategy

The literature databases Web of Science, Scopus, EMBASE, and PubMed were searched and used to locate studies on the use of AS in the treatment of burn patients. Articles published until May 2018 were included in the database search. However, as AS transplantation dates back to before the beginning of the 20th century, the initial date of publication was not indicated. This decision also reduced the risk of losing studies that are older, but valuable, due to good methodological quality.

For the definition of the search terms (MeSH terms), the PICO strategy was used.[26] In this study, it was decided not to use the acronyms C and O for definition of mesh terms. This search strategy was adopted to increase the number of selected articles. In addition to the MeSH terms, all entry terms found during MeSH search were also used, such as

Population (P): Burns OR Burns [MeSH] OR Burn

AND

Intervention (I): Biological dressings OR Biological dressings [MeSH] OR Biologic Dressing OR Biologic Dressings OR Dressing, Biologic OR Dressings, Biologic OR Dressing, Biological OR Biological Dressing OR Dressings, Biological OR Heterograft Dressings OR Dressing, Heterograft OR Dressings, Heterograft OR Heterograft Dressing OR Xenograft Dressings OR Dressing, Xenograft OR Dressings, Xenograft OR Xenograft Dressing OR Porcine Xenograft Dressings OR Dressing, Porcine Xenograft OR Dressings, Porcine Xenograft OR Porcine Xenograft Dressing OR Xenograft Dressing, Porcine OR Xenograft Dressings, Porcine OR Pig Skin Dressings OR Dressing, Pig Skin OR Dressings, Pig Skin OR Pig Skin Dressing OR Amniotic Membrane Dressings OR Amniotic Membrane Dressing OR Dressing, Amniotic Membrane OR Dressings, Amniotic Membrane OR Homograft Dressings OR Dressing, Homograft OR Dressings, Homograft OR Homograft Dressing OR Allograft Dressings OR Allograft Dressing OR Dressing, Allograft OR Dressings, Allograft.

Selection criteria

The following inclusion criteria were used for selecting the studies: randomized clinical trial (RCT) or nonrandomized clinical trial (NRCT) when comparing AS to another skin substitute in the treatment of burns; articles published in full between any date until May 2018; indexed in the Web of Science, Scopus, EMBASE, and PubMed databases, without language limitation.

The exclusion criteria included articles, editorials, and/or letters published in the form of abstracts; unpublished studies; case reports; case series; and cross-sectional, observational, and experimental animal studies. Studies that did not include burn patients and studies that compared the use of AS with cultured epithelia, of autologous or allogeneic origin, were also excluded.

Initially, AS was always considered as a temporary skin substitute. With the experience gained over time with the use of this material in third-degree lesions, it has been found that depending on the type of the tissue preservation process, it may permanently remain on the burn bed.[19,27] Considering these two possibilities, we opted to select only studies in which AS was used as a temporary coverage for partial- and full-thickness burns. In partial-thickness burns, AS was used to simulate wound healing (reepithelization), and in deep burns, it was used as a mechanism of wound bed preparation to increase autograft integration or as a "sandwich" on the autografts to stimulate autograft take.

Study selection

Initially, only the titles and abstracts from clinical trials assessing the use of AS in burn treatments were screened and read. The full text of all the prescreened studies was read and selected, and, subsequently, used for constructing the final sample of articles that met all of the inclusion criteria. The article selection committee consisted of a plastic surgeon (AOP) and research methodology specialist (VFC). In the event of a tie, a third individual, also a plastic surgeon (CI), was asked to settle the impasse.

Data collection

The reviewers extracted the following data from the articles: author, year, study type, sample size, mean age, % TSBA, etiology, lesion thickness, type of clinical trial, AS processing, comparative method, follow-up time, and the following outcomes: wound healing, autograft take percentage, final scar quality, and mortality.

In particular, skin substitutes including human cadaveric allograft can be used for different indications in different settings. To facilitate the understanding of the collected data about the function of the allogenic skin and the other skin substitutes in the selected studies, we chose to classify them using a classification of cutaneous substitutes. There is no universally agreed classification of skin substitutes, but to facilitate, we chose to use a classification described in our service,[28] which takes into account three factors to classify the substitute: layer to be replaced (E — epidermal, D — dermal, or C — dermal—epidermal components), durability (T — temporary or P — permanent), and origin of the product (b — biological, s — synthetic, or bs — biosynthetic).

Risk of bias assessment

In RCTs, the risk of bias was assessed using the Cochrane Handbook criteria for bias risk judgments.[29] For NRCTs, the risk of bias analysis was performed with ROBINS-I.[30]

Statistical analysis

The RevMan 5.3 program[31] was used for performing the statistical analysis and constructing forest plots. It was possible to perform meta-analysis only on two outcomes: number of patients who healed and percentage of graft take.

For dichotomous variables (i.e., number of patients who healed), the relative risk was used as a measure of effect, with a fixed effects model and a confidence interval of 95%. For continuous variables (i.e., autograft percentage), the effect of the mean difference was used, with a random effects model and a confidence interval of 95%.

Results

Initially, 5800 studies were identified; however, after reading titles and abstracts and removing any duplicates, only 142 papers remained. The contents of all the articles were read in full, and it appeared as though 19 studies would be included in the systematic literature review. However, it was found that two of the studies (Schurr et al.[32] and Centanni et al.[33]) presented different outcomes on the same clinical trial (#NCT006118839). The samples and methodologies employed in both articles were similar; however, the outcomes were different. Thus, during the analysis, these two articles were considered as a single study, and the final number of articles selected for review was 18 (Figure 1).

Characterization of selected studies

In all the studies, AS may be classified as C (dermal-epidermal replacement), T (temporary), and b (biological origin). Thirteen studies[32-44] had used AS for wound bed preparation or cover autografts (sandwich technique) to increase integration. Five[45-49] had studied the effect of AS to stimulate wound healing (re-epithelization) on partial-thickness burns. Only one[50] evaluated both aspects in different kinds of patients (partial- and full-thickness burn patients).

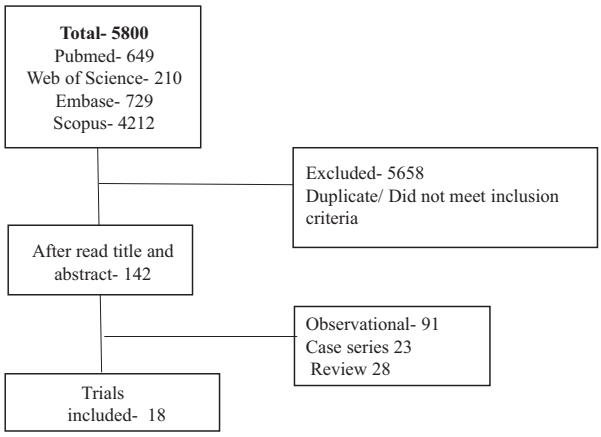

Figure 1 Flowchart of included studies.

With regard to the characterization of the populations studied in the selected articles, Supplementary Table 1 shows that the vast majority of the studies used small sample sizes and included both adults and children. There is also a considerable deal of variation in % TBSA of the patients. Almost all of the trials tested burned patients, exclusively, but two of them (Centanni et al.[33] / Schurr et al.[32] and Berry et al.[50]) evaluated pressure-induced wounds.

Supplementary Table 2 summarizes the methodologies used by the authors and shows that 12 of the clinical trials are RCTs and the other 6 are NRCTs. Additionally, one study was an uncontrolled clinical study,[49] and the remaining studies used a control group or performed a self-control, by dividing the wound in half. With regard to the types of treatments compared to AS, it was observed that there was a tremendous diversity, which included simple burn exposure to the employment of modern laboratory-developed skin substitutes.

The follow-up time varied widely, some authors monitored the patients only during the acute stage (14 days), while others, particularly those assessing scar quality and pliability, followed up patients for up to two years. It is also worth noting that there was a huge disparity in the number of outcomes studied. In all, 27 different outcomes were presented, with the most frequently studied outcomes being healing, graft take percentage, and scar quality.

Risk of bias assessment for randomized clinical trials

In Figure 2, the consensual evaluations of the article selection committee for each domain of the selected RCTs ($N = 12$) are presented. The bias risk assessment of the RCTs showed that the selected studies presented a considerable risk for bias in all of the analyzed domains (Figure 3).

Risk of bias assessment for nonrandomized clinical trials

Among the six studies analyzed, five were determined to have a serious or critical risk of bias, which was evidenced

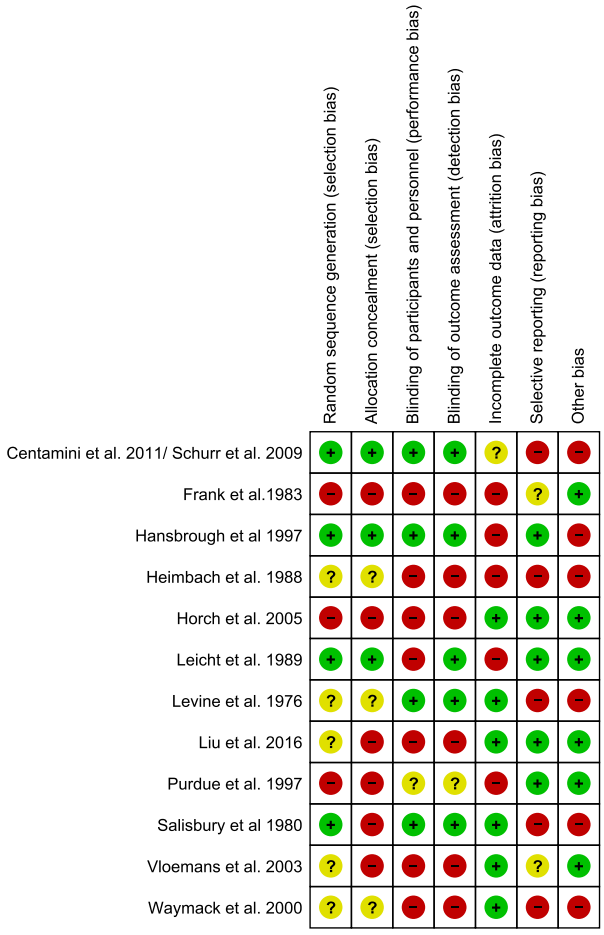

Figure 2 Summary of risk of bias in the selected RCTs: The symbols represent the apparent risk of bias associated with the different domains of each study included in the sample and are based on the judgment and expertise of the reviewers.

by methodological flaws in the formulation of the studies (Supplementary Table 3). Only one of them (Salisburry[42]) was found to have a moderate risk of bias; however, it was a small study that only evaluated one outcome (evaporative loss).

Outcomes and meta-analysis

Supplementary Table 4 shows the results of the different studies in relation to the outcomes of interest in this review: healing, graft take percentage, scar appearance, and mortality.

Outcome - healing

The data related to the wound healing outcome were presented in two ways: as a dichotomous event (the wound healed or not) and as the time required for epithelialization or lesion restoration.

With regard to articles containing dichotomous data, four of them had complete data for total number of treated, healed, and unhealed patients, which made them candidates for meta-analysis. However, the article of Liu et al.[51] was excluded on meta-analyses because the skin substitute served as a stimulus for the integration and growth of autografts and not for re-epithelization; hence, it is not possible to compare it with other studies selected for meta-analyses.

In Figure 4, the black diamond symbol nearly coincides with the x-axis at 1, with most of the confidence interval being positioned on the AS side of the plot.

Regarding the re-epithelialization time, it would be necessary to present the standard deviations to be able to construct the forest plot. Only one study[51] presented complete data; however, as mentioned previously, this study investigated a skin substitute that functions to stimulate the integration and growth of autologous grafts and not as a stimulator of the healing process. Therefore, it was not possible to perform a meta-analysis.

Outcome - graft take percentage

In this outcome, we studied the effect of skin substitutes used temporarily to stimulate the autograft integration. Only three articles ([33,38,51]) contained all of the necessary data. In Figure 5, it is observed that the graft take percentage is quite similar between the AS group and the other skin substitutes. However, based on the confidence interval, there was a slight predominance for AS.

Outcome - scar appearance

There are a number of ways for evaluating the outcome of scar appearance, which prevented any kind of meta-analysis for this outcome. For example, each author used a different set of criteria to assess whether there was a hypertrophic scar formation or not. In fact, most of the authors who analyzed this outcome, when comparing AS with other skin substitutes, did not perceive a statistical difference in hypertrophic scar formation, between groups (Supplementary Table 4).

Outcome - mortality

Three articles presented data related to patient mortality; however, two of these studies (Heinbach et al.[39] and Purdue et al.[40]) were self-controlled, with the intervention and control being performed on the same wound. However, in these studies, mortality cannot be related to any treatment, as the patient receives both. The third study (Naoum et al.[46]) showed that in the AS group, there was 0% mortality (0/16), while in the group receiving sulfadiazine, there was 23% mortality (3/13) (Supplementary Table 4).

Discussion

AS transplantation is a very old clinical procedure and has generated more than 5800 publications on the subject. However, there is an apparent shortage in the number of clinical trials comparing AS with other skin substitutes. This can be seen as slightly discerning, as clinical trials are fundamental in ensuring that good clinical management practices are maintained at an adequate level.[52] Unfortunately, most of the studies in this area are case reports, case series, observational studies, and reviews.

A majority of studies (13) have sample sizes that contained less than 50 participants. It is highly probable that the high cost of skin substitutes is a substantial barrier to

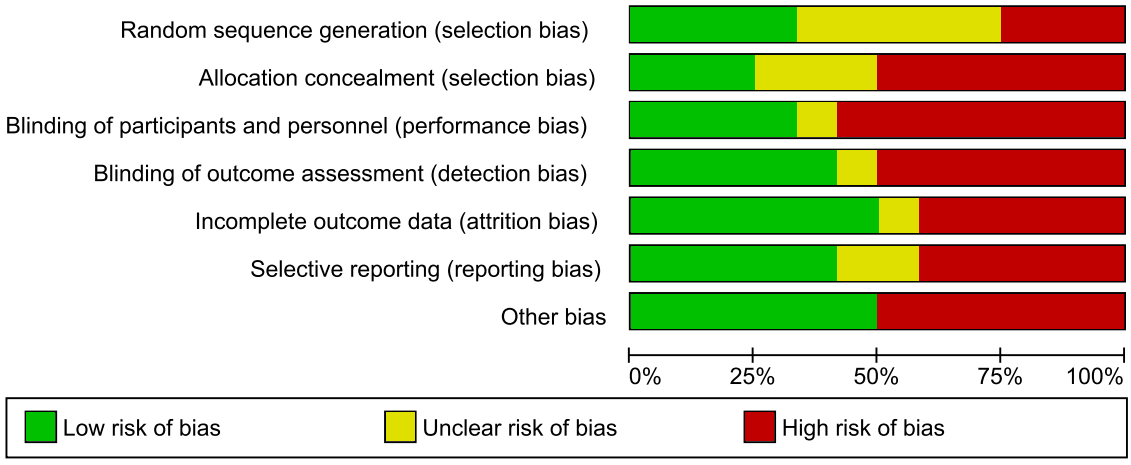

Figure 3 Summary of the risk of bias in the selected NRCTs: Each risk of bias domain is presented as a percentage of all included studies and based on the judgment and expertise of the reviewers.

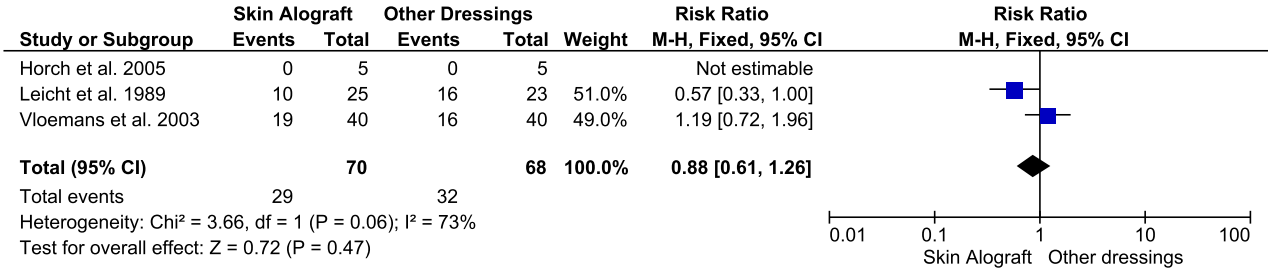

Figure 4 Forest plot for wound healing.

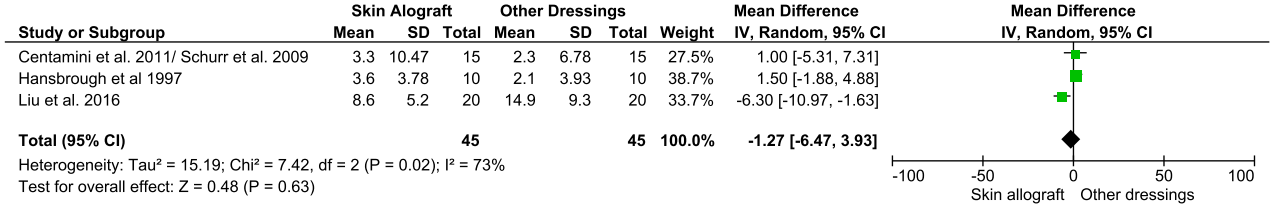

Figure 5 Forest plot for graft take percentage.

conducting these types of trials. Consequently, an inadequate sample size impairs the ability to generate statistically significant results.[53] Additionally, the selected studies enrolled patients that included a mixture of children and adults. This variability in age can interfere with the production of reliable results. For example, with regard to the scarring process, in younger patients, healing usually occurs more rapidly because of the greater number of fibroblasts, increased production of collagen, and accelerated formation of granulation tissue.[54]

Another point that stands out is the considerable variability in% TBSA (0.5 to 95%) of the patients and the use of AS in both partial- and full-thickness burns. Initially, skin substitutes were created with the purpose of being utilized in patients with a limited amount of autogenous graft donor area. However, years of clinical practice, especially that associated with AS, stimulated doctors to discover new skin substitutes and clinical uses thereof. In addition to serving as a temporary skin substitute for more superficial burns, reducing mortality rates, stimulating re-epithelialization, preventing bacterial infection, and reducing water loss, these skin substitute products can also prepare the wound bed, increase the chances of the graft taking, and improve the esthetic quality and pliability of the final scar.[5] Thus, these substitutes can be used to treat patients suffering from large second-degree burns, as well as in patients with smaller third-degree burns, with the ultimate goals being a reduction in graft loss and an improvement in final scar quality.

We initially intended to restrict the selection of studies to a specific %TBSA, but we would lose many results. Despite the increased number of skin substitute studies, we know very little about the indications of each of them in different clinical situations. In this review, we chose to group the studies according to two main outcomes: wound healing (reepithelization), more common in superficial burns, and improvement in autografts integration, through wound bed preparation or as a sandwich graft, used more in deeper burns.

In the clinical trials that included a predominance of patients with second-degree burns, it was more common for the comparative group to use a more simple dressing such

as hydrocolloids, silver sulfadiazine, or simple exposure to air, although in some studies, more complex substitutes such as Biobrane® and porcine skin were employed. On the other hand, in the case of third-degree burns, the comparative group usually utilized a more complex skin substitute such as Integra®, Dermagraft®, and Apligraft®. In these cases, as third-degree burns tend to evolve more frequently with cicatricial hypertrophy, graft take percentage, wound bed preparation, and final scar quality were being evaluated.

The technique used to process the allogeneic tissue can also interfere with the clinical outcome in burn treatment and whether the tissue can integrate to the wound or not. In fact, in a retrospective observational study, researchers investigated the effect of cryopreserved and glycerol-preserved skin on the treatment of burn victims and compared them in terms of mortality rate and days of hospitalization. The study demonstrated that the results obtained with cryopreserved skin were better than those obtained with glycerol.[55] However, as the purpose of this systematic review was to compare the outcomes associated with AS with those of other available skin substitutes, all of the articles that used AS were included, regardless of the manner in which the tissue was preserved (i.e., refrigeration, cryopreservation, freeze-drying, or glycerol-preserved). However, it is important to remember that this review selects only clinical studies that use temporarily AS for burns and discard those of permanent integration.

With regard to mortality, only three articles evaluated this outcome and two of them[39,40] employed a self-controlled methodology. Although there is less risk of bias with this methodological approach in evaluating the evolution of the wound, it is not possible to use these data for analyzing and comparing mortality data as the patient receives both treatments. Thus, when analyzing mortality, it is essential that two groups exist and that all comparisons are made with different individuals receiving different treatments. Naoum et al.[46] study was the only one for which a mortality analysis could be performed. The authors reported a 0% mortality (0/16) for patients treated with AS and a 23% mortality (3/13) for patients treated with sulfadiazine. However, it should be pointed out that this was an NRCT, with a small sample size, and was considered to have a critical bias level. Observational studies suggest that AS can reduce mortality in patients suffering from large burns. In a retrospective study, it was reported that there was a concomitant reduction in mortality and improvements in patient care, when AS was used as a temporary skin substitute.[56]

In the meta-analysis for wound healing outcome, included studies compared AS with dressings such as hydrocolloid, silver sulfadiazine, and simple air exposure in second-degree burns. There was a slight advantage for using AS because most of the confidence interval fell on that side of the axis. However, the results obtained with these new dressings are based on studies with poor methodological quality and did not perform the AS comparison with patients who experienced extensive second-degree burns. The slight apparent improvement in the healing process, associated with AS, questions whether expensive skin substitutes should be used for treating second-degree burns. For example, in these cases, there are other more cost-effective alternatives such as biosynthetic dressings (impregnated with silver or silicone based), which have previously been shown to provide desirable results.[57]

Regarding the graft take percentage, AS was compared to a cellular porcine skin,[51] StrataGraft®[33], and Dermagraft®[38], and graft take percentage was evaluated in previously debrided full-thickness burns. In Figure 5, the black diamond symbol abuts the transverse axis, with most of the confidence interval positioned on the AS side of the plot. However, the confidence interval of this graph is smaller, meaning that the probability of differences existing in the stimulation of the graft take process is lower between the AS group and other substitutes.

Regarding the final quality of the scar, the results are even more inconclusive. A solution to this problem would be to use a scar scale such as the Vancouver Burn Scar Score.[58] In the current study, only one article (Waymack et al.[59]) used this scale; however, only two patients, out of 40 participants, received AS. Despite the poor results of the selected studies, there is an increase in the number of articles being published on the topic, which demonstrates the importance of skin substitutes in improving the quality and appearance of the scar, especially on the hands.[60]

The main limitation of this study is the low methodological quality of the primary studies selected. In the RCT risk of bias analysis, none of the evaluated domains had a low risk of bias (i.e., greater than 50% of the total). In the NRCT risk of bias evaluation, the situation was even worse. Only one article[42] was considered to have moderate risk, as assessed by ROBINS-I, while the others had a serious or critical risk of bias. This poor methodological quality not only reduces the amount of evidence but also hinders the execution of comparative analyses between/among groups.

In the present study, it was found that studies comparing AS with other skin substitutes were insufficient in providing a standardized protocol for indicating the use of these materials in the treatment of burn patients. Thus, consequently, the choice of skin substitute for burn treatment continues to be based on the empirical personal experience of each surgeon. Furthermore, based on the available evidence, it is unclear why AS is considered the gold standard for skin transplantations, as other skin substitutes performed similarly in some of the clinical trials. Ultimately, the choice of skin substitute comes down to cost, availability, and experience.

Conflict of interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2019.04.013.

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