



Hyaluronic acid covers in burn treatment: a systematic review*

Coberturas de ácido hialurônico no tratamento de queimaduras: revisão sistemática
Coberturas de ácido hialurónico en el tratamiento de quemaduras: revisión sistemática

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ABSTRACT

Objective: To evaluate the effectiveness of hyaluronic acid in the healing of partial thickness burns. **Method:** Systematic review of randomized controlled trials on the use of hyaluronic acid for the topical treatment of skin burns, based on recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. **Results:** Two randomized controlled trials that analyzed 143 patients with partial thickness burns and/or deep partial thickness burns were selected. They compared the application of hyaluronic acid 0.2% associated to silver sulfadiazine 1% 5g/cm² versus silver sulfadiazine 1% 5g/cm² alone for the outcome of complete healing. **Conclusion:** This review emphasizes the need for new well-designed randomized controlled trials to establish the therapeutic relevance of hyaluronic acid with respect to the healing of burns of partial thickness or deep partial thickness.

DESCRIPTORS

Hyaluronic Acid; Burns; Wound Healing; Evidence-Based Nursing; Review.

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INTRODUCTION

Wounds are defined as a solution of continuity of the skin or adjacent tissues originating from physical, chemical or thermal damage⁽¹⁾. The treatment of these injuries involves the use of covers, an advanced method⁽²⁾ that uses products ideally obtained from biological components that are minimally handled, non-toxic, hypoallergenic and enable removal of the product without further tissue damage. Moreover, the covers must provide a moist environment, promote gas exchange, prevent bacterial development, control excessive exudate⁽³⁾, and maintain constant local temperature⁽⁴⁾ without need for routine change⁽⁵⁾.

In this context, hyaluronic acid stands out as a new technology for treating dermal and epidermal injuries. It consists of biological materials derived from components extracted of the extracellular matrix⁽⁶⁾. Hyaluronic acid has essential features to any biological coverage such as biocompatibility and biodegradability, plus it does not induce immunogenicity⁽⁷⁻⁸⁾.

As a therapeutic agent, hyaluronic acid is used in numerous applications, among which eye surgery, tissue reconstruction⁽⁹⁻¹⁰⁾, degenerative and inflammatory joint diseases, synovial fluid replacement, release of chemical agents in surgical implants, systems of encapsulation and controlled release of drugs and topical cosmetics⁽¹¹⁾. In local treatment of wounds, it is used in the form of cream, gel, or impregnated gauze to promote healing⁽¹²⁾.

Burns are a peculiar group of wounds treated with hyaluronic acid. They are a traumatic injury resulting from direct or indirect action of thermal energy on the human body that leads to tissue destruction. Burns may develop into a chronic debilitating condition with morbidity and significant mortality⁽¹³⁾.

Etiologically, burns are triggered by various agents, such as heat, radiation, cold, radioactivity, electricity, friction or exposure to chemicals⁽¹⁴⁾. The mechanism or etiology of injuries, grade, depth of tissue involvement, and extent of body surface area burned are considered for their classification⁽¹⁵⁾.

The aim of the treatment is mainly to accelerate healing and control the excessive deposition of collagen in scar tissue to prevent the occurrence of contractures and keloids⁽¹⁶⁾. Suitable topical therapy of a burn injury considers using products to control bacterial growth, remove devitalized tissue and promote healing⁽¹⁷⁾. The selection of dressings is based on the effects on healing, ease of application and removal of the product, the cost of treatment, and patient's comfort⁽¹⁸⁾.

The successful treatment leads to recovery of physiological function, alleviation or elimination of symptoms such as pain or itching, and aesthetic and functional restoration of injuries without the occurrence of hypertrophic scars or keloids⁽¹⁹⁾.

Given the impact of burns on survivors and the complexity of treatment, it is necessary to search for scientific evidences to support the best clinical decision. Thus, the objective of this review is to evaluate the effectiveness of hyaluronic acid in the healing of burns of partial thickness or deep partial thickness.

METHOD

This is a systematic review of randomized controlled trials based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions proposed by the Cochrane Collaboration. A systematic review is a type of secondary study performed from a defined research question. By using the question, the aim is to identify, evaluate, select and synthesize evidence from primary studies that meet the predefined eligibility criteria⁽²⁰⁾.

For the elaboration of the research question was used the acronym PICO⁽²¹⁾ (P – population or problem, I – intervention; C – comparison; O – outcomes) in which: P – Hospitalized patients with partial thickness burns and/or deep partial thickness burns, regardless of the mechanism of injury, depth, location or body surface area burned; I – use of hyaluronic acid; C – Different concentrations and formulations of hyaluronic acid, placebo, standard treatment, and other types of dressings; O – Healing. Thus, the research question was: *What is the effectiveness of hyaluronic acid in the healing process of burns of partial thickness and/or deep partial thickness in hospitalized patients?*

This review included randomized controlled trials, published or not, with any sample size that contemplated the adoption of hyaluronic acid in the treatment of skin burns of partial thickness or deep partial thickness, regardless of the mechanism of injury, depth, location or body surface area burned in hospitalized children, adolescents, adults and elderly.

Studies involving other etiologies of wounds, not limited to the use of hyaluronic acid intervention, and other study designs that not randomized trials were excluded.

The relevant studies were found by searching in the following electronic databases: Medical Literature Analysis and Retrieval System Online/PubMed (MEDLINE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Literature in the Health Sciences in Latin American and the Caribbean (LILACS), Cochrane Central Register of Controlled Trials (CENTRAL) and Excerpta Medica Database (EMBASE). There were no restrictions concerning the date of publication or language.

Complementarily, was performed a manual search for gray literature, which consists of studies not controlled by scientific or commercial publishers, such as government reports, theses, dissertations and abstracts published in conference proceedings. The reference lists of the clinical studies found were examined to identify potentially eligible studies that were not found in the search strategy.

We selected the descriptors and their synonyms in Portuguese and English for the search of primary studies in the previously established databases: *Medical Subject Headings (MeSH) – hyaluronic acid, or hyaluronate, or hyaluronan; and burn, or burns; and randomized controlled trial; Health Sciences Descriptors (DeCS) ‘ácido hialurônico’; and ‘queimaduras or queimadura’; combined using Boolean operators AND, OR, added to truncation symbols that formed the basis of the search equation, later adapted to the specifications of each base.*

For inclusion, the abstracts of the identified studies were assessed blindly and independently by two reviewers, who applied the eligibility criteria and selected the relevant studies. In case of disagreement, a third reviewer was requested. In the first consensus meeting, the selected studies were assessed in full with application of eligibility criteria. Subsequently, in the second consensus meeting were defined the studies included and excluded from the review. The Kappa coefficient⁽²²⁾ was used to assess the interobserver agreement with score range between 1 (complete agreement) and -1 (complete disagreement). During consensus meetings, there was support from a third reviewer for disagreements between reviewers.

The selection was composed of two phases: a) first screening, evaluation of the titles and abstracts of all identified studies; b) reading in full: evaluation of the full text.

For data extraction, was developed a form to summarize information of the studies, which included identification, method, participants, clinical characteristics, intervention, comparison, clinical outcomes, ethical issues and financing.

The assessment of methodological quality of the selected studies was conducted by the Cochrane Collaboration's tool for assessing the risk of bias in randomized controlled trials available in the Review Manager version 5.3⁽²³⁾. In this evaluation, the studies were judged as 'low risk of bias', 'high risk of bias', and 'unclear risk of bias' for the domains: generation of random sequence (selection bias), allocation concealment (selection bias), blinding of participants and professionals (performance bias), blinding of outcome assessors (detection bias), incomplete outcomes (attrition bias), and selective outcome reporting (reporting bias).

There was no conflict of interest nor any kind of funding for conducting this review.

RESULTS

The search strategies resulted in 69 studies. Of this amount, 20 were published in more than an electronic base and 45 did not meet the inclusion criteria. Thus, four studies were evaluated in full. After independent analysis by two reviewers, two studies were included in this review, as shown in Figure 1. The score of interobserver concordance rate (Kappa) on the inclusion or exclusion of studies was 0.877 ($p = <0.001$), indicating agreement reliability between the two reviewers.

Fifteen articles were eliminated because they were experimental studies, five were in vitro studies, six assessed the treatment of corneal burns, two of the tympanic membrane, an application of intra-articular hyaluronic acid, an application of intra-abdominal hyaluronic acid, and a study about rhinoplasty. A case report about burn treatment with dermal substitute was also excluded, as well as a pilot study on hyaluronic acid, a study evaluating the pH of burns, one on the use of Aloe Vera in thermal injuries, four studies that applied dermal matrix, a systematic review about diabetic foot, a systematic review on hyaluronic acid, a study on venous ulcers, a study using dressings with silver sulfadiazine, and a nonrandomized controlled trial. One of the pre-selected studies was not obtained with full text, so it was excluded of the review.

In the second consensus meeting, a previously selected controlled trial was excluded by applying hyaluronic acid in the graft donor area, and not in the burns. Another study was excluded because it did not present the specific results of hyaluronic acid for the treatment of burns among the various types of injuries included.

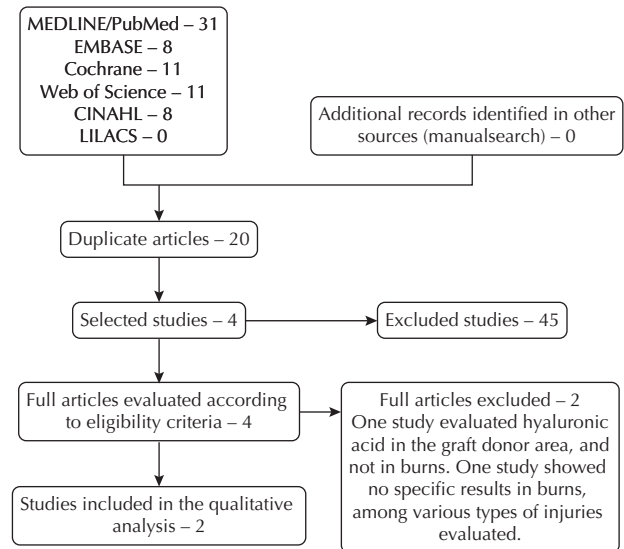


Figure 1 – Flowchart of identification, selection and inclusion of studies – Curitiba, PR, Brazil, 2016.

In the individual assessment of methodological quality (Figure 2), a randomized controlled trial presented the domain *assessment of outcomes* classified as unclear risk of bias because information about the blinding of outcome assessors was not evident in the report⁽²⁴⁾. In turn, the other study did not have any domain with low risk of bias⁽²⁵⁾.

	Generation of random sequence (selection bias)	Allocation concealment (selection bias)	Blinding of participants and professionals (performance bias)	Blinding of assessment of outcomes (detection bias)	Incomplete outcomes data (attrition bias)	Selected reports (reporting bias)
COSTAGLIOLA; AGROSI, 2005	+	+	+	+	+	+
KOLLER, 2004	+	+	+	?	+	+

Legend: + 'low risk of bias'; - 'high risk of bias'; ? 'unclear risk of bias'.

Figure 2 – Individual assessment of the methodological quality of the studies included in the systematic review – Curitiba, PR, Brazil, 2016.

In the first domain, both studies describe the use of a computer program to obtain the allocation sequence. For allocation concealment, the authors only provided information describing the clinical similarity between participants in controls and intervention groups.

The blinding of participants and professionals was declared in both studies through the standardization of packaging and compatibility characteristics of topical agents (Intervention – Hyaluronic acid cream 0.2% and silver sulfadiazine 1% 5g/cm², or Control – silver sulfadiazine 1% 5g/cm²).

In the domain *assessment of outcomes*, one of the articles does not state where analytical data were treated, which configures unclear risk of bias for this domain⁽²⁴⁾.

In both evaluated studies, the selection of outcome reports or incomplete information were not identified in the results. All the outcomes mentioned in the methodology were reported in the analysis, thus categorizing *low risk of bias* for this domain.

Chart 1 shows the selected studies with the respective references, publication year, country, design and number of patients evaluated.

Chart 1 – Studies selected according to the reference, year, country, design and number of patients – Curitiba, PR, Brazil, 2016.

Study	Reference	Year/Country	Design/number of patients
Koller ⁽²⁴⁾	Koller J. Topical treatment of partial thickness burns by silver sulfadiazine plus hyaluronic acid compared to silver sulfadiazine alone: a double-blind, clinical study. <i>Drugs Exp Clin Res</i> , 2004; 5, 183-190.	2004/Slovakia	Randomized controlled trial double blind/ n=33
Costagliola and Agrosi ⁽²⁵⁾	Costagliola M, Agrosi M. Second-degree burns: a comparative, multicenter, randomized trial of hyaluronic acid plus silver sulfadiazine vs. silver sulfadiazine alone. <i>Curr Med Res Opin</i> , 2005; 21(8): 1235-40.	2005/France, Croatia, Slovenia and Germany	Multinational controlled clinical trial, multicenter, double blind/ n=111

A study included patients aged between 18 and 80 years, mean of 35 (±14.5) years for the intervention group, and 40.7 (±11.6) years in the control group. There were no clinical or laboratory abnormalities, except for those caused by the thermal injury⁽²⁴⁾.

The second study included patients aged between 18 and 75 years, mean of 38.2 (±12.4) years in the intervention group, and 38.5 (±13.7) years in the control group. The follow up of one patient was lost during the study⁽²⁵⁾. The clinical inclusion and exclusion criteria were identical in both studies.

In relation to injuries, randomized patients of the first study had partial thickness burns or deep partial thickness burns, with between 5 and 11% of body surface area burned⁽²⁴⁾. Patients of the second study had burns of partial thickness and/or deep partial thickness with body surface area burned of less than 5%⁽²⁵⁾.

Regarding comparison, both studies evaluated the association between hyaluronic acid cream 0.2% and silver sulfadiazine 1% 5g/cm² versus silver sulfadiazine 1% 5g/cm² applied weekly for 28 days. The primary outcome was the average healing time⁽²⁴⁻²⁵⁾.

A study showed 8.167 (± 2.684) days as mean time for complete healing of wounds in the intervention group, while in the control group 13.067 (± 5.203) days were needed for the total healing⁽²⁴⁾. This difference was statistically significant (p = 0.001) in favor of the intervention group. In another clinical trial study, the average healing time was 9.5 (± 1.28) days in the intervention group compared to 14 (± 0.51) days in the control group⁽²⁵⁾.

DISCUSSION

The aim of this systematic review was to evaluate the effectiveness of hyaluronic acid in complete healing of partial thickness and/or deep partial thickness burns compared to other covers and/or solutions. In this context, 143 patients were analyzed in two randomized controlled trials, randomly distributed for the outcome of complete healing.

There was a statistically significant difference in mean healing time in favor of intervention groups compared to controls⁽²⁴⁻²⁵⁾. The inconsistency test demonstrated by the Review Manager 5.3 program of the Cochrane Collaboration showed heterogeneity of 97%, hence it was not possible to perform the meta-analysis between studies for the outcome of *average healing time*.

In a systematic review, were evaluated topical formulations containing hyaluronic acid for the treatment of chronic wounds of various etiologies, such as thermal injury, venous ulcers and diabetic foot. It was found that the product promotes healing when compared to other treatments⁽²⁶⁾.

In a randomized controlled trial, the efficacy of hyaluronic acid in the treatment of venous ulcers was compared to a neutral carrier. The primary outcome was the percentage reduction of the wound size at 45 days. It was found that the reduction of the ulcer surface area was significantly higher in the intervention group (73 ± 4.6%) versus the control group (46 ± 9.6%) (P = 0.011). The number of healed ulcers in the intervention group was higher at day 45 (31% vs. 9%, respectively) and day 60 (37% vs. 16%, respectively) (P<0.05)⁽¹²⁾.

Specifically in thermal injuries, a cohort study with 60 patients with partial thickness burns found an average reduction of 50% in the size of the wound in the first five follow up days of combined application of hyaluronic acid with zinc. Complete healing occurred in 93.3% of the sample after 21 days of follow up, with an average healing time of 10.5 days⁽²⁷⁾.

A retrospective study evaluated the clinical efficacy of grafting with goat dermal matrix combined with hyaluronic acid in five patients with extensive full thickness burns. Patients were submitted to nine skin micrograft applications covering 17 members. The average time of devitalized tissue peeling was 17.7 (± 2.7) days and the hospitalization time was 115 (± 27) days. After 72 (± 6) days, the residual wound was less than 5% of body surface⁽²⁸⁾.

In experimental studies, hyaluronic acid demonstrates superiority compared to other covers, with respect to shorter time of wound healing and histological characteristics such as improved elasticity and higher microvascular density⁽²⁹⁻³⁰⁾.

When hyaluronic acid is applied in wounds, there is improved water retention, which favors a suitable environment for the formation of collagen and elastin, and allows the cells to proliferate and differentiate, accelerating the healing process⁽³¹⁾.

Furthermore, the anti-inflammatory properties of hyaluronic acid influence the healing, preventing the conversion of wound⁽³²⁻³³⁾ and formation of hypertrophic scars or keloids⁽³⁴⁾.

Another relevant aspect for the application of hyaluronic acid is the fact of biomaterial being a non-immunogenic substance. An experimental study was conducted to determine the skin tolerance to topical application of hyaluronic acid in full thickness injuries (35% of the body

surface area), and it showed the substance was well tolerated and there were no adverse or side effects⁽³⁵⁾.

CONCLUSION

The results of this systematic review show the lack of sufficient evidence in the literature to support the use of hyaluronic acid in the topical treatment of burns. Given the above, this review emphasizes the need for well-designed randomized controlled trials to establish the therapeutic relevance in the healing of partial thickness burns or deep partial thickness burns, and thus incorporate hyaluronic acid to clinical practice.

However, the topical action of the combination of hyaluronic acid and silver sulfadiazine showed significantly favorable response in relation to the average healing time of partial thickness burns or deep partial thickness burns. In addition, there was no occurrence of adverse effects or side effects, thus suggesting the possibility for the clinical use of the product in terms of effectiveness and safety.

RESUMO

Objetivo: Avaliar a efetividade do ácido hialurônico na cicatrização de queimaduras de espessura parcial. **Método:** Revisão sistemática de ensaios clínicos randomizados sobre a utilização de ácido hialurônico no tratamento tópico de queimaduras de pele, baseada nas recomendações do *Cochrane Handbook for Systematic Reviews of Interventions*. **Resultados:** Foram recuperados dois ensaios clínicos randomizados que analisaram 143 pacientes portadores de queimaduras de espessura parcial e/ou espessura parcial profunda, comparando a aplicação de Ácido Hialurônico 0,2% associado à Sulfadiazina de Prata 1% 5g/cm², versus Sulfadiazina de Prata 1% 5g/cm² isolada, para o desfecho cicatrização completa. **Conclusão:** Esta revisão enfatiza a necessidade de novos ensaios clínicos randomizados bem delineados para estabelecimento da relevância terapêutica do ácido hialurônico no que tange à cicatrização de queimaduras de espessura parcial ou espessura parcial profunda.

DESCRITORES

Ácido Hialurônico; Queimaduras; Cicatrização; Enfermagem Baseada em Evidências; Revisão.

RESUMEN

Objetivo: Evaluar la efectividad del ácido hialurónico en la cicatrización de quemaduras de espesor parcial. **Método:** Revisión sistemática de ensayos clínicos randomizados acerca de la utilización de ácido hialurónico en el tratamiento tópico de quemaduras de piel, basada en las recomendaciones del *Cochrane Handbook for Systematic Reviews of Interventions*. **Resultados:** Fueron recuperados de los ensayos clínicos randomizados que analizaron 143 pacientes portadores de quemaduras de espesor parcial y/o espesor parcial profundo, comparando la aplicación de Ácido Hialurónico al 0,2%, asociado con la Sulfadiazina de Plata al 1% 5g/cm², versus Sulfadiazina de Plata al 1% 5g/cm² aislada, para el resultado de una cicatrización completa. **Conclusión:** Esta revisión subraya la necesidad de nuevos ensayos clínicos randomizados bien planteados para el establecimiento de la relevancia terapéutica del ácido hialurónico en lo que se refiere a la cicatrización de quemaduras de espesor parcial o espesor parcial profundo.

DESCRIPTORES

Ácido Hialurónico; Quemaduras; Cicatrización de Heridas; Enfermería Basada en la Evidencia; Revisión.

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