

# Clinical use of topical hyaluronan for promoting corneal wound healing: a systematic review

Uso clínico do ácido hialurônico tópico para promover a cicatrização de feridas na córnea: uma revisão sistemática

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## ABSTRACT

**Introduction:** Hyaluronan/hyaluronic acid based therapies are commonly used for treating corneal injuries in the clinic; however, there is a lack of consensus on whether hyaluronic acid promotes corneal wound healing. This systematic review critically evaluated peer-reviewed publications describing the clinical use of topical hyaluronic acid for treating corneal injuries.

**Methods:** Unfiltered searches were conducted to identify peer-reviewed publications describing the clinical use of topical hyaluronic acid for treating various forms of corneal injuries using PubMed® and the University of Houston Library online databases. Citations were screened and data extracted according to the PRISMA checklist.

**Results:** A total of 16 articles using topical hyaluronic acid administration for treating corneal injuries were included. The concentration of hyaluronic acid used ranged from 0.1% to 2%, and the frequency of administration ranged from a single dose to 24 times daily. Overall, the studies identified that hyaluronic acid successfully promotes corneal wound healing, with no reports of any adverse effects.

**Conclusions:** The available literature shows that hyaluronic acid promotes corneal wound healing, with no reported adverse effects. There is a lack of consensus on the optimal dosage of hyaluronic acid that should be used for treating corneal wounds in the clinic.

Prospero Registry - CRD42023440356

## RESUMO

**Introdução:** As terapias à base de ácido hialurônico são comumente utilizadas na clínica para o tratamento de lesões de córnea; no entanto, não existe consenso se o ácido hialurônico realmente promove a cicatrização da córnea. Esta revisão sistemática avaliou criticamente artigos científicos que descrevem o uso clínico do ácido hialurônico tópico no tratamento de lesões de córnea.

**Métodos:** Foram realizadas buscas não filtradas para identificar artigos que descrevem o uso clínico do ácido hialurônico tópico no tratamento de diferentes tipos de lesões de córnea, utilizando as bases de dados PubMed® e os recursos on-line da Biblioteca da Universidade de Houston. As citações foram triadas e os dados, extraídos de acordo com o checklist PRISMA.

**Resultados:** Um total de 16 artigos sobre o uso de ácido hialurônico tópico para o tratamento de lesões de córnea foram incluídos. A concentração de ácido hialurônico utilizada variou de 0,1% a 2%, e a frequência de administração variou de dose única a 24 vezes por dia. De modo geral, os estudos identificaram que o ácido hialurônico promove a cicatrização da córnea, sem relatos de efeitos adversos.

**Conclusões:** A literatura disponível demonstra que o ácido hialurônico promove a cicatrização de feridas na córnea, sem relatos de efeitos adversos. No entanto, ainda não há consenso sobre a dosagem ideal a ser utilizada clinicamente para o tratamento dessas feridas.

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## INTRODUCTION

The cornea forms the outer layer of the eye, and, as such, is prone to external insults and injuries. Corneal injuries are a serious medical condition that can cause severe pain, vision loss, and functional limitations.<sup>(1)</sup> A loss of corneal transparency is the fifth leading cause of blindness worldwide.<sup>(1)</sup> In Emergency Departments, eye injuries account for 3% of all cases, with 80% of those being due to corneal epithelial damage.<sup>(2,3)</sup> Studies have estimated that about 20% of the population will suffer ocular trauma in their lifetime.<sup>(4)</sup> Elective eye surgeries like LASIK and SMILE often involve corneal abrasions or incisions, which are associated with corneal complications. Many other surgical interventions also require that the cornea be breached, such as photorefractive keratectomy, cataract surgery, pterygium surgery, or vitrectomies, and are also associated with potential complications. Therefore, effective methods for promoting corneal wound healing are necessary for restoring vision following corneal injuries and surgical interventions.

Available treatments for managing corneal epithelial defects include lubrication, bandage contact lens, antibiotics, steroids, and oral supplements. Among these interventions, topical hyaluronan (HA), also called hyaluronic acid, in the form of eye drops, gels, contact lens, and bandages has become a mainstay option for treating corneal injuries with the purpose of promoting wound healing and providing symptom relief through lubrication.<sup>(5,6)</sup> HA is a non-sulfated glycosaminoglycan that is essential for supporting tissue integrity, development, and repair. HA has been shown to be expressed in various major compartments in the ocular surface, including the cornea, limbus, vitreous humor, aqueous humor, trabecular meshwork, and Meibomian gland.<sup>(7)</sup> In the cornea, HA is expressed primarily in the limbal epithelial stem cell niche (LSCN) and is upregulated in and around the wound bed after injury.<sup>(8)</sup> Additionally, HA is naturally present in the tear fluid that continuously bathes the ocular surface.<sup>(9)</sup> HA has been shown to regulate various major processes that are central to corneal wound healing, including corneal epithelial proliferation, migration, wound closure, inflammation, and lymphangiogenesis.<sup>(8,10-14)</sup>

In recent years, the use of HA based therapies in the clinic for ophthalmic purposes has grown exponentially.<sup>(6,15)</sup> HA-based therapies are very well tolerated and topical application to the ocular surface has been widely used for promoting corneal wound healing for over a decade; however, there is still no consensus on whether HA actually promotes wound healing. Further, guidelines are lacking

for the optimal route, frequency of administration, and, more importantly, the form and concentration of HA that should be used. Therefore, the primary objective of this systematic review was to evaluate all available literature on the clinical use of HA for treating patients with various corneal injuries in order to determine the efficacy of HA for promoting corneal wound healing, and to summarize the range of treatments that are used in the clinic. This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

## METHODS

### Search strategy and study eligibility criteria

This review was carried out in accordance with the PRISMA 2020 statement.<sup>(16)</sup> We classified the current report as a systematic review, which was prospectively registered with PROSPERO (ID=CRD42023440356).

A structured search strategy was developed to identify relevant citations across two online databases: PubMed® (National Library of Medicine, Bethesda, MD, USA) and databases and electronic resources provided by the University of Houston Libraries. The search strategy did not use filters and included the following combination of keywords: “hyaluronan or hyaluronic acid and corneal wound healing”, “hyaluronan or hyaluronic acid and corneal injury”, and “hyaluronan or hyaluronic acid and ocular surface” (Figure 1). The initial search was conducted on April 3, 2023. In order to ensure the inclusion of all studies reported, no chronologic filters were used at the time of the search. All search results were compiled and uploaded onto Microsoft Excel, and duplicates removed yielding 246 records (Supplementary Material - Table 1S). The titles, abstracts and, when necessary, full texts were initially screened by an investigator and categorized based on the contents of the studies (type of injury, species, form of HA administration). Another investigator then served as an independent reviewer that thoroughly and objectively screened all titles, abstracts and full text to carry out data validation. The investigator that had screened the manuscripts then carried out data extraction from the included studies and the one that had categorized the manuscripts screened the extracted data and carried out data validation. Any disagreements or queries were resolved by a third and fourth investigator. During the search stage, the first and the second investigators were masked to the purpose of the study in order to prevent any potential biases. Additionally, the titles and abstracts were screened

by both the first and the second investigators individually and independently to eliminate any potential of conformity bias. Since the focus of the systematic review was to evaluate the efficacy of HA for promoting wound healing in human subjects, all studies utilizing animal models were excluded. Thereafter, full-text screening to identify eligible articles was completed by two investigators (the first and the second investigator), and findings compiled using Microsoft Excel Version 16.80 (Microsoft 365). If the full text was unavailable, efforts were made to reach the primary, last and corresponding authors to obtain a copy. If we were unable to obtain the full text, the studies were excluded. Finally, articles were only included if they were published in English. The list of selected papers that were included in our review is provided as Supplementary Material - Table 2S.

### Study selection and data extraction

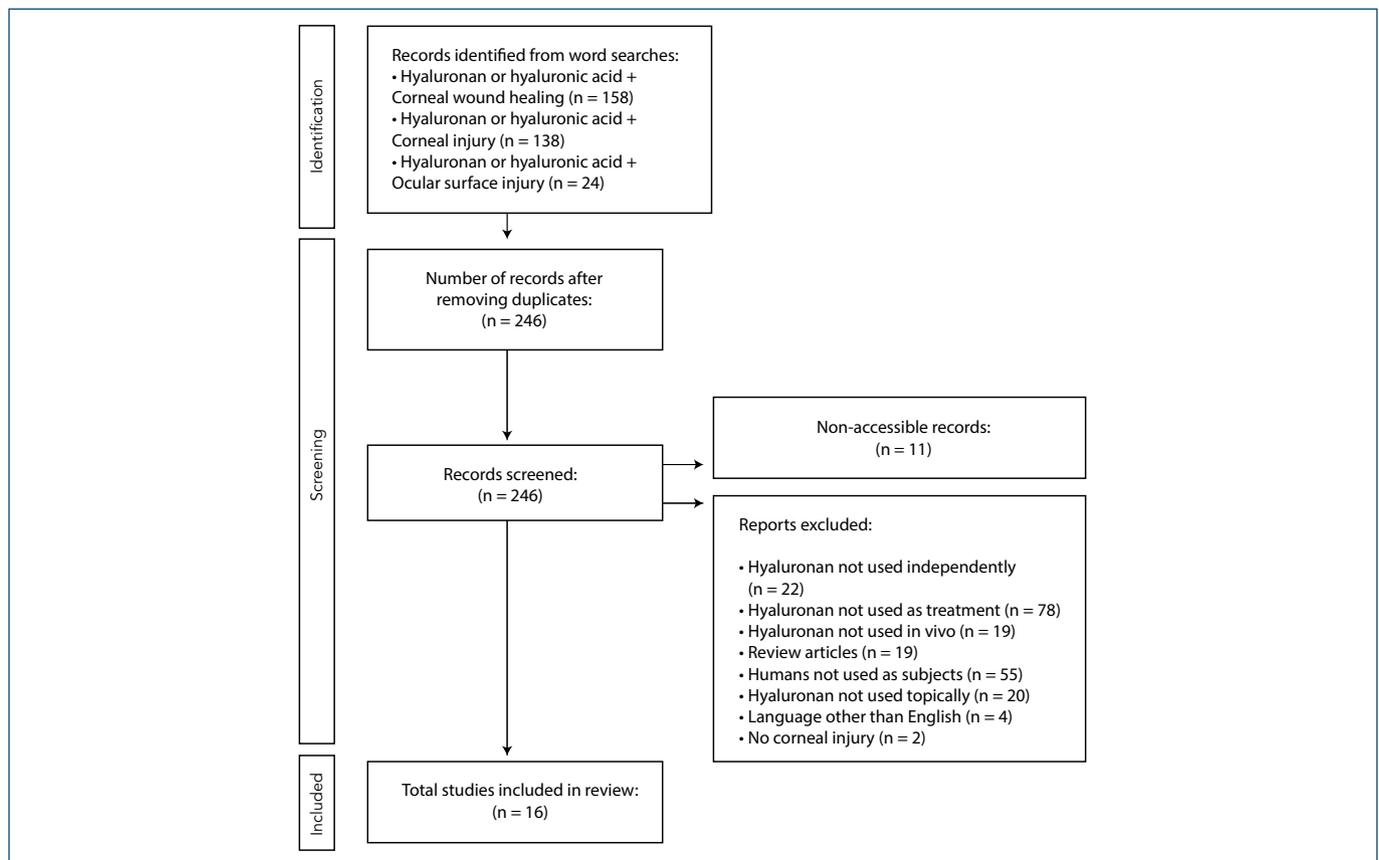
Studies met inclusion criteria if they encompassed each of the following: topical HA was used, HA was used to treat a form of ocular injury, and the study was in human subjects. Any study that did not meet all three criteria was excluded. Further exclusion criteria used were non-English

publications, solely in vitro studies, case reports, studies with solely animal models, review articles, and studies where HA was administered for non-ocular reasons or administered non-topically. A total of sixteen articles were retrieved addressing the use of topical HA in human subjects for treating corneal injuries (Supplementary material - Table 2S).

The full text articles were screened, and a data extraction following PRISMA checklist.<sup>(16)</sup> Data that was extracted included type of injury or surgical intervention, patient demographics, molecular weight of the HA used, concentration of HA used, form of administration, what was used as the vehicle control, treatment regimen, and treatment outcome. Additionally, information on the year of publication, and total number of citations in PubMed® and Google Scholar were also obtained and compiled.

### Data analysis

One author conducted the data extraction, and a second author carried out an in-depth confirmation and validation of the extracted data. Two authors further reviewed the data extraction. The extracted data was then analyzed and compiled by three investigators. Graphs were assembled in GraphPad Prism 7.04.



**Figure 1.** A PRISMA flow diagram outlining the study selection process, including the inclusion and exclusion criteria.

## RESULTS

### Details of excluded studies and summary of studies included

Overall, 16 studies were included with publication dates spanning from 1995 to 2022, with only 4 published before 2013, 4 published between 2014 and 2017, and 9 after 2018 (Figure 2A). To expand on the reliability of the selected studies, a search was performed to determine the number of citations that each of the selected studies had. Data from Google Scholar and PubMed® were used and shown in Figure 2B. The average number of citations for the studies were 2.5 on PubMed®, and 19 on Google Scholar (Figure 2B). Cellini et al.<sup>(17)</sup> and Schulze et al.<sup>(18)</sup> were the most cited articles while Tsuji et al.<sup>(19)</sup> Wei et al.<sup>(20)</sup> and Chaidaroon et al.<sup>(21)</sup> were the least cited (Figure 2B).

### Characteristics of the studies included

Of the 16 studies included in this systematic review, ten studies concluded that HA successfully promoted wound healing,<sup>(17,21-29)</sup> while two studies reported no significant effect.<sup>(20,30)</sup> Overall, HA was used to treat a variety of injuries or surgical interventions, as outlined in table 1. The most common procedure treated was a vitrectomy, followed

by photorefractive keratectomy (PRK), epithelium-off for CXL, and pterygium surgery.

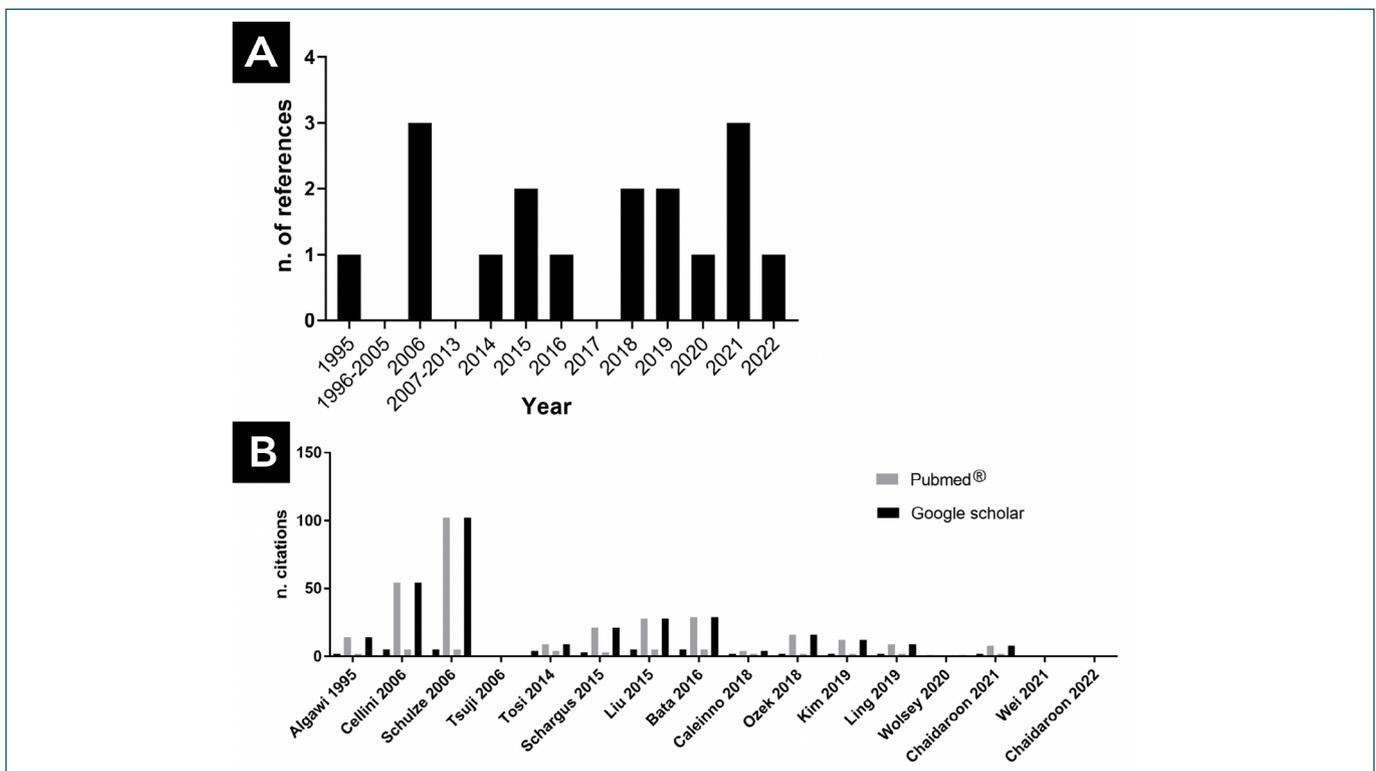
**Table 1.** Types of injuries and/or surgical interventions treated with hyaluronan

Type of injury or surgical intervention	Number of studies	Reference
PRK	2	Wolsey et al. <sup>(22)</sup> and Algawi et al. <sup>(30)</sup>
Laser refractive surgery	1	Calienno et al. <sup>(23)</sup>
Keratoconus patient undergoing epithelium-off for CXL	2	Ozek et al. <sup>(31)</sup> and Bata et al. <sup>(32)</sup>
Cataract surgery	1	Cellini et al. <sup>(17)</sup>
Pterygium surgery	2	Chaidaroon et al. <sup>(21,24)</sup>
Dry eye disease	1	Kim et al. <sup>(25)</sup>
Vitrectomy	3	Schulze et al., <sup>(18)</sup> Ling et al. <sup>(26)</sup> and Tosi et al. <sup>(27)</sup>
Drug toxicity	1	Liu et al. <sup>(28)</sup>
Laser subepithelial keratomileusis	1	Tsuji et al. <sup>(19)</sup>
Traumatic abrasion	1	Wei et al. <sup>(20)</sup>
Persistent epithelial defect	1	Schargus et al. <sup>(29)</sup>

PRK: photorefractive keratectomy, CXL: corneal cross-linking

### Experimental design and outcome of the studies included

Overall, two studies investigated the efficacy of HA for promoting wound healing following PRK<sup>(22,23,30)</sup> and one after laser refractive surgery<sup>(22,23,30)</sup> with similar patient cohorts. Specifically, 40 patients (23 females) ranging from ages 21 to 53 years in Algawi et al.,<sup>(30)</sup> to 100 patients



**Figure 2.** (A) Identified research papers using hyaluronan to promote corneal wound healing in patients with various types of corneal injuries and organized based on the year they were published, ranging from 1995-2022. (B) The number of times each of the identified research papers were cited using either PubMed® or Google Scholar was collated, organized by date and represented as a graph.

(57 women) with ages ranging from 23 to 39 years old in Calienno et al.,<sup>(23)</sup> and 45 patients (23 male) ranging from 22-45 in Wolsey et al.<sup>(22)</sup> The treatment regimen and form of HA administration varied significantly among the three studies. A single topical application of 10mg/ml HA (of unknown molecular weight) was used in Algawi et al.,<sup>(30)</sup> 0.2% high molecular weight hyaluronan (HMWHA) eye drops four times daily for 90 days was used in Calienno et al.<sup>(23)</sup> and cross-linked HA ocular bandage gel (OBG) 8 times a day for 3 days, followed by 4 times daily for 11 days was used in Wolsey et al.<sup>(22)</sup> The single administration of HA in Algawi et al.<sup>(30)</sup> provided no significant effect on pain or rate of wound healing, whereas both Calienno et al.<sup>(23)</sup> and Wolsey et al.<sup>(22)</sup> reported significant improvement in corneal wound healing and increased rate of re-epithelialization. Further, a case report described a 30-year-old male that underwent LASIK surgery with a corneal epithelial flap detachment occurring after 20 days.<sup>(19)</sup> He was treated with 0.3% HA eye drops (unknown molecular weight) with levofloxacin, and bandage contact lenses. Ten days after detachment, the epithelial detachment had completely healed.<sup>(19)</sup> The authors speculated HA had a role in promoting corneal epithelial wound healing in this patient.<sup>(19)</sup>

Overall, two studies investigated the efficacy of HA for promoting wound healing following epithelium-off corneal cross-linking,<sup>(31,32)</sup> with similar patient cohorts, 40 patients (31 males) with a mean age of 31 with a standard deviation of 10 years<sup>(32)</sup> and 23 patients (13 females) ranging from the ages of 19 to 35.<sup>(31)</sup> As for the treatment regimen, Bata et al. studied the effects of a new matrix therapy agent in wound healing compared to 0.1% HA (of unknown molecular weight) eye drops every other day starting immediately after surgery.<sup>(32)</sup> The study indicated that matrix therapy promoted significantly faster wound healing than the HA therapy alone (4.4 vs 6.1 days). Unfortunately, this study lacked a control group and the composition of the matrix therapy, and whether it contained HA was not stated. As for the study by Ozek and colleagues, eye drops containing unpreserved trehalose 30 mg/mL and HA 1.5 mg/mL (Thealoz Duo<sup>®</sup>) were applied in one eye, while unpreserved HA 0.15% (Eye Still<sup>®</sup>) was applied to the other six times daily.<sup>(31)</sup> The study found faster corneal re-epithelialization after corneal cross-linking with the combination of trehalose and HA when compared to HA alone. However, a vehicle control group for the independent use of HA was also not included in this study.

Two studies investigated the efficacy of HA for promoting wound healing of corneal epithelial defects

following pterygium surgery,<sup>(21,24)</sup> with similar patient cohorts, 50 patients (25 females) with ages ranging between 20 and 60 years in Chaidaroon et al.,<sup>(24)</sup> and 86 patients (47 males) with ages ranging between 20 and 70 years in Chaidaroon et al.<sup>(21)</sup> In Chaidaroon et al.,<sup>(24)</sup> a single topical application of 2% HMWHA (MW of  $1.8 \times 10^6$  Da) was administered following the procedure and compared to a placebo control, and the authors found that HA significantly promoted wound healing. A follow-up study by the same group compared two different concentrations of HA. 0.18% of HMWHA (MW of  $1.2 \times 10^6$  Da) and 0.3% HMWHA (MW of  $1.0 \times 10^6$  Da) administered as eye drops four times daily for 3 days. The authors found that both concentrations improved wound healing, however the higher concentration promoted wound healing to a higher extent.

A number of studies investigated the effects of HA on epithelial defects from various other causes. A single study investigated the effects of HA on corneal epithelial damage after cataract surgery.<sup>(17)</sup> In this study, 30 patients (18 female) with ages ranging from 62 and 74 years (mean of 68.3 years) were included comparing the use of 0.2% HA and 10  $\mu$ g NGF eye drops every 2 hours for 2 weeks, followed by four times for another week.<sup>(17)</sup> Although there was no significant difference in endothelial cell count between the groups, corneal thickness was significantly greater in the HA treated group.<sup>(17)</sup> The effects of HA were also investigated on improving wound healing following epithelial debridement associated with pars plana vitrectomy.<sup>(26)</sup> For such, 30 patients with ages ranging from 43 and 79 years (mean age of  $61.2 \pm 7.9$  years) were organized into three groups: group 1 included 10 patients (10 eyes) with diabetes who received 0.18% HA eye drops 4 times daily (every 6 hours) over a 5-day period. Group 2 included ten diabetic patients (ten eyes) without HA treatment. Group 3 included ten non-diabetic patients (ten eyes) without HA treatment. The study found that topical HA treatment significantly improved corneal wound healing and accelerated complete corneal wound resurfacing in diabetic patients.<sup>(26)</sup> A study investigated the effects of HA on promoting wound healing following epithelial debridement after vitrectomy for proliferative vitreoretinopathy.<sup>(27)</sup> For such, 40 patients were organized into the following groups, topical treatment of hydroxypropyl methylcellulose (HPMC) 2% (20 patients mean age  $63.55 \pm 10$ ) and 1.2% HA (20 patients mean age  $69.7 \pm 12$ ). The HA treated group presented a significantly faster rate of wound healing with less frequent complications. Another study compared the effects of HA with autologous serum

on corneal abrasions for better intraoperative visualization with pars plana vitrectomy.<sup>(18)</sup> For such, 23 diabetic patients (15 men) with a mean age of 64.8 years were randomly assembled into two groups, one group (10 patients) was treated hourly with HA drops (Vislube) and the other group (13 patients) was treated with autologous serum. The study concluded that autologous serum promoted a faster rate of epithelial closure when compared to HA; however, unfortunately, a control group was not included in this study. A single study investigated the effects of HA on persistent epithelial defects (PED) and sterile corneal ulcers (CU).<sup>(29)</sup> This study included 17 patients with PED and 30 patients with sterile CU. Patients were treated with either 0.1% HA or 5% albumin eye drops eight times a day until achieving complete epithelium closure. In the PED group, both forms of treatment showed equal efficacy, while in the CU group, the albumin treated group had a lower recurrence rate ( $p = 0.03$ ).<sup>(29)</sup> The effects of HA on promoting wound healing following traumatic corneal abrasion was also investigated.<sup>(20)</sup> A total of 56 patients with traumatic corneal abrasion were divided into an untreated control group with 27 patients (17 male) with mean age  $38.5 \pm 9.4$  and a group treated with 0.3% HA eye drops for 3 months including 29 patients (17 female) with a mean age of  $36.5 \pm 12.8$ . The study found that long-term use of HA does not provide additional benefit during the recovery of hemidesmosome junctions.<sup>(20)</sup>

A single study investigated the effect of oral supplementation of HA in addition to topical HA administration for improving the comfort and outcome for patients with dry eye disease (DED).<sup>(25)</sup> For such, 54 patients, >18 years of age were distributed into the treatment group (6 males and 18 females) with a mean age of  $48.6 \pm 13.0$  receiving topical 0.15% HMWHA eye drops 5 to 6 times daily along with oral HA supplementation given once daily for 3 months compared to the control group (22 females) with a mean age of  $53.29 \pm 10.8$  and receiving topical 0.15% HMWHA eye drops alone 5-6 times daily for 3 months.<sup>(25)</sup> The study found that a combination of oral and topical HA is more effective in improving corneal epithelial wound healing and related symptoms in patients with DED when compared to topical HA alone.<sup>(25)</sup> A single study evaluated the effects of HA on patients receiving benzalkonium chloride (BAC)-preserved antiglaucoma medications.<sup>(28)</sup> For such, 58 patients (40 female) with an age range of 35 to 63 were organized into a group receiving unpreserved 0.3% HA eye drops three times a day for 90 days compared to a control group receiving phosphate buffered saline (PBS). The study found that HA significantly protects

the cornea from damage caused by BAC-preserved antiglaucoma medications, improving goblet density, Ocular Surface Disease Index (OSDI) scores, staining scores, tear film break up time, and conjunctival epithelium.<sup>(28)</sup>

## Correlation of outcome and the type of hyaluronan and concentration used in the studies included

The collected articles were then organized based on the type of HA used, and, surprisingly, only three articles specified the type of HA that was used, and in all three the investigators used HMWHA.<sup>(21,23,25)</sup> All three studies that specified that HMWHA was used demonstrated positive outcomes after administration of HA. No articles specified the use of low molecular weight hyaluronan (LMWHA). The remaining 13 articles did not specify the molecular weight of HA used (Table 2).

**Table 2.** Molecular weight of hyaluronan used in the studies

Molecular weight of hyaluronan used	Number of studies	Reference
High molecular weight hyaluronan	3	Chaidaroon et al., <sup>(21)</sup> Calienno et al. <sup>(23)</sup> and Kim et al. <sup>(25)</sup>
Low molecular weight hyaluronan	0	N/A
Unspecified molecular weight	13	Cellini et al., <sup>(17)</sup> Schulze et al., <sup>(18)</sup> Tsuji et al., <sup>(19)</sup> Wei et al., <sup>(20)</sup> Wolsey et al., <sup>(22)</sup> Chaidaroon et al., <sup>(24)</sup> Ling et al., <sup>(26)</sup> Tosi et al., <sup>(27)</sup> Liu et al., <sup>(28)</sup> Schargus et al., <sup>(29)</sup> Algawi et al., <sup>(30)</sup> Ozek et al., <sup>(31)</sup> Bata et al. <sup>(32)</sup>

The studies were then stratified based on the concentration of HA used. Eight different HA concentrations were used, ranging from 0.1% to 2%. One study did not specify the concentration of HA used.<sup>(22)</sup> Two studies used 0.1% HA,<sup>(29,32)</sup> which was the lowest HA dose used among all studies, and of these only Schargus et al.<sup>(29)</sup> reported a positive outcome on corneal wound healing. The other study did not have a control group so was inconclusive as to whether 0.1% HA was enough to promote wound healing.<sup>(29,32)</sup> The study by Ozek et al. used 0.15% HA, which did not report that HA promotes corneal wound healing since there was also a lack of a control group.<sup>(31)</sup> In another study, Kim et al. used 0.15% HA, which promoted corneal wound healing. Three studies utilized 0.18% HA to treat corneal injuries, with each of these studies reporting HA promoted corneal wound healing.<sup>(18,21,26)</sup> Two studies reported the use of 0.2% HA to treat corneal injuries, with both reporting HA promoted corneal wound healing.<sup>(17,23,25)</sup> Four studies used 0.3% HA to treat corneal injuries.<sup>(19-21,28)</sup> with three of them reporting HA promoted corneal wound healing,<sup>(19,21,28)</sup> while one study reported HA did not promote corneal wound healing.<sup>(20)</sup> One study used 10 mg/mL HA, which is 1% HA, which was reported to not

promote significant corneal healing.<sup>(30)</sup> One study used 1.2% HA<sup>(27)</sup> and one study used 2% HA, with both reporting HA promoted corneal wound healing.<sup>(24)</sup>

**Table 3.** Concentration of hyaluronan used in the studies

Concentration of hyaluronan used (%)	Number of studies	Reference
0.1	2	Schargin et al. <sup>(29)</sup> and Bata et al. <sup>(32)</sup>
0.15	1	Ozek et al. <sup>(31)</sup>
0.18	1	Chaidaroon et al. <sup>(21)</sup>
0.2	3	Cellini et al. <sup>(17)</sup> Calienno et al. <sup>(23)</sup> and Kim et al. <sup>(25)</sup>
0.3	4	Tsuji et al. <sup>(19)</sup> Wei et al. <sup>(20)</sup> Chaidaroon et al. <sup>(21)</sup> and Liu et al. <sup>(28)</sup>
1	1	Algawi et al. <sup>(30)</sup>
1.2	1	Tosi et al. <sup>(27)</sup>
2	1	Chaidaroon et al. <sup>(24)</sup>

## DISCUSSION

The cornea is continuously subjected to external insults, and HA is often used in the clinic as a first line of therapy for promoting corneal wound healing; however there is no standard of therapy or consensus on the form or concentration of HA that should be used. This systematic review aimed to analyze the available literature to assess whether HA is effective in promoting corneal wound healing following distinct types of corneal injuries, and to compile and compare the spectrum of HA treatment regimens that are used in the clinic to treat various forms of corneal injuries and abrasions.

Out of total 16 articles included in this systematic review, ten concluded that HA promotes corneal wound healing, whereas two studies found no statistical increase in the rate of wound healing when compared to the control group. The remaining four studies were inconclusive regarding the effects of HA on corneal wound healing since they did not include a control group to be able to assess the effects of HA. Curiously, in these four studies, HA was actually used as the “control” group for their study.<sup>(18,19,31,32)</sup> Specifically, the studies aimed to verify if their proposed novel therapeutics were able to promote wound healing to a higher extent than HA, regarded as the standard of care. The included studies presented a wide range of HA regimens used for treating an array of injuries, with the concentration of HA ranging from 0.1% to 2%, which means a 20-fold difference in the concentration of HA used. In terms of the form of HA used, only three studies disclosed this information, while all other studies made no mention of the molecular weight of HA. Of the studies that did report the form of HA used, all used HMWHA. The molecular weight of HA dictates its physiological functions, with HMWHA shown to promote

homeostasis, promote tissue regeneration and to have anti-inflammatory properties, aiding in the resolution of immune responses.<sup>(33,34)</sup> In contrast, LMW-HA has been shown to promote inflammation and induce angiogenesis.<sup>(35,36)</sup> Further, studies have demonstrated that HMWHA increases cell migration, wound healing, and reduces the cytotoxicity of ultraviolet B (UVB) radiation, while LMWHA does not.<sup>(37)</sup> HMWHA also has been shown to reduce the cytotoxic effects of NaOH on corneal cells and promotes corneal wound healing.<sup>(38)</sup> Our lab has shown that all forms of HA can promote corneal wound healing in a concentration dependent manner; however, HMWHA is more efficacious at promoting cell viability and proliferation.<sup>(11)</sup> Moreover, a number of studies on the effects of different forms of HA on skin wound healing and in treating osteoarthritis demonstrate that HMWHA is the optimal form of HA with highest therapeutic properties.<sup>(39,40)</sup> Thus, the consensus is that HMWHA is the optimal form of HA for treating corneal wounds in the clinic. Therefore, it is surprising that most studies using HA to treat corneal wounds in the clinic do not report the form of HA used, and, importantly, future studies should ascertain they are using the correct form of HA prior to initiating the study. Given the unique characteristics of each form of HA, it is critical that studies state the molecular weight of HA being used to be able to understand the significance of the findings and the possible therapeutic applications for each form of HA. Additionally, HA is often used in the clinic for its characteristics of providing lubrication. Importantly, the lubricating properties are directly proportional to increasing molecular weight of HA, so ultra-HMWHA in the excess of 4000 kDa could be considered in lieu of HMWHA and LMWHA. Curiously, we recently showed that there is a huge variation in the form and concentration of HA in over-the-counter eye drops.<sup>(11)</sup> Thus, it is imperative to establish the concentration and optimal molecular weight of HA to be used for each clinical application and to establish guidelines as to what form and concentration of HA should be used for treating distinct corneal pathologies.

A surprising finding of this systematic review was the lack of consistency in the HA treatment regimens that are used in the clinic. In addition to the variability in concentration and form of HA used in the different studies, there was also drastic variability in the frequency of application and duration of treatment. Therefore, given the lack of consistency in the HA treatment regimens used, no conclusions could be drawn as to which treatment regimen was most efficacious for promoting corneal wound healing. In order to advance our knowledge in

the clinical use of HA as a topical therapy for promoting wound healing in the clinic and improve the standard of care, standardized HA treatments that are currently being used must be established. This will allow objective assessments to be made on what the optimal treatment regimen is, reducing treatment variability and enabling physicians to prescribe the most effective HA formulations. Developing a standard guideline for HA application would allow future studies to stratify findings based on form of HA, concentration of HA, dosages, frequency of treatment and duration of treatment. Based on the findings of this systematic review, the concentration in which HA is being used as a topical therapy in the clinic ranges from 0.1% to 2%. Curiously, a study in rabbits carried out a concentration-dependent investigation on the effects of HA of 800 to 1,400 kDa on corneal wound healing.<sup>(41)</sup> This study found that there was a concentration-dependent effect of HA on wound healing, with higher concentrations promoting wound healing to a higher extent.<sup>(41)</sup> They found that 0.2% of HA had the maximum effect and that above that concentration there was no added benefit.<sup>(41)</sup> Further, the effects of HA of HMWHA of different ranges were compared, namely 800 to 1,400, 1,400 to 2,000, and 2,000 to 2,600 kD, and no differences were noted between HMWHA within these different ranges.<sup>(41)</sup>

Currently modified forms of HA have been developed with the goal of enhancing certain physiological properties of HA. For example, crosslinked-HA (X-HA) that is a chemically modified form of HA where the molecules are linked together following the treatment with chemical cross-linking agents. When compared to HA, X-HA presents higher stability, enhanced viscosity, improved mechanical strength, and prolonged retention time on the ocular surface.<sup>(42-44)</sup> X-HA has been shown to successfully promote corneal wound healing in animal models and in the clinic.<sup>(45-47)</sup> Other chemical analogs of HA include sulfonated HA, acetylated HA, chitosan, alginate, carboxymethyl cellulose, and heparan sulfate analogs. Analogs of HA are mostly developed for increased stability, for tailored viscoelastic properties, for reducing the cost, and/or for modified bioactivity. HA analogs are widely used in medications and cosmetics, and many studies have explored their use in promoting corneal wound healing. Chitosan is a polymer obtained from alkaline/enzymatic digestion of chitin<sup>(48)</sup> that is made up of repeating units of N-acetyl-d-glucosamine and d-glucosamine linked by  $\beta$ -(1-4) glycosidic bonds with similar structural characteristics to glycosaminoglycans.<sup>(49)</sup> Both Chitosan and HA have been shown to promote wound

healing;<sup>(49)</sup> however, when blended, they improve corneal epithelial reconstruction significantly and restore cornea transparency and thickness, serving as an effective and rapid combinatorial way for corneal wound healing.<sup>(50)</sup>

HA has been used in a clinical setting for promoting wound healing since 1995; however, there has been a surge of studies involving HA-based therapies for treating corneal pathologies in recent years, with a significant increase in studies published after 2018. This systematic review provides an overview of the efficacy of HA-based therapies for promoting wound healing, revealing that, overall, HA based therapies are beneficial for promoting wound healing, with no studies reporting any negative effects. Importantly, this systematic review identified a major flaw in most studies when reporting the form of HA utilized, with most studies neglecting to provide key information on the molecular weight of the HA utilized. In a clinical setting, it is vital for physicians to utilize HA formulations with a defined molecular weight since different forms of HA have significantly different physiological functions. It is noteworthy that the combined studies that were included in this review demonstrated variability in several aspects, including patient demographics, type of injury, frequency of HA administration, concentration of HA used, outcome measurements, and follow-up schedules, providing further limitations in the ability to cross-compare these studies to draw overall conclusions on the effects of HA on corneal wound healing. Finally, future studies should be dedicated to first establishing a dose response for HA-based therapies, in order to enable the research community to establish a consensus on the optimal concentration of HA that should be used for promoting corneal wound healing.

## CONCLUSION

This review serves as a groundwork for future research initiatives that focus on refining hyaluronan-based therapies and establishing guidelines based on scientific evidence for medicinal use in corneal wounds. The limitations in the current literature shed light on the importance of reporting the form of HA used in the studies, and for reaching a consensus on the concentration of HA that should be used for each clinical application. Importantly, HA is a highly stable compound that can be stored at room temperature for long periods with no associated side effects, and therefore is an optimal blanket first line therapy. Through a collaborative effort, future studies must establish an optimal dosage, form and treatment frequency for optimizing HA therapies.

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## SUPPLEMENTARY MATERIAL

### Table 1S

A full list of articles that was compiled after the initial search.

<https://www.rbojournal.org/wp-content/uploads/2025/08/RBO-2024-0156-RA-st1.pdf>

### Table 2S

The final list of the articles that were included in the systematic review.

<https://www.rbojournal.org/wp-content/uploads/2025/08/RBO-2024-0156-RA-st2.pdf>