Title

Efficacy of 0.1% crosslinked hyaluronic acid, coenzyme Q10 and vitamin E in the management of dry eye disease in menopause patients receiving antidepressants.

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Keywords

Crosslinked hyaluronic acid; coenzyme Q10; dry eye; eyedrops; antidepressant

Purpose

The purpose of this study is to test non-inferiority of a lower dose of crosslinked hyaluronic acid (CLHA) to a higher dose of carmellose eye drop in menopause patients receiving antidepressant treatments.

Methods

This prospective, double-blind, single-center study enrolled sixty female patients. Mean age was 63.25 ± 9.13 years. We examined patients with Schirmer I, breakup time (TBUT) and the ocular surface disease index (OSDI) at the first visit. Tear A eyedrops were formulated with crosslinked hyaluronic acid, coenzyme Q10 and vitamin E. Control tear B was formulated with carmellose sodium. Posology was two and five times, respectively.

Results

After two months of treatment, the tear A obtained 14.12 ± 7.47 score points for OSDI ($t = 11.74$, $P < .01$), and tear B obtained 19.46 ± 10.03 score points ($t = 7.59$, $P < .01$). The tear A obtained 13.77 ± 7.78 score points for Schirmer test ($t = 0.88$, $P > .05$), and tear B obtained 14.20 ± 8.62 score points ($t = 2.92$, $P < .01$). The tear A obtained 8.30 ± 2.08 seconds for TBUT ($t = 15.50$, $P < .01$), and tear B obtained 7.23 ± 2.40 seconds ($t = 8.79$, $P < .01$).

Conclusions

Lower total daily dose of crosslinked hyaluronic acid eyedrops obtained similar efficacy results in terms of tear stability and subjective dry eye sensation than higher carmellose total daily dose. A lower total daily dose of crosslinked eyedrops was sufficient to achieve better dry eye disease management compared to carmellose.

Keywords

Crosslinked hyaluronic acid; coenzyme Q10; dry eye; eyedrops; antidepressant

Introduction

Dry eye is a multifactorial disease of tears and the ocular surface that manifests as discomfort, vision disturbances and instability of the tear film, which may damage the ocular surface.(1) It generally affects bilaterally and chronically. Dry eye is generally accompanied by an increase in the osmolarity of the tear film and inflammation of the ocular surface.(2) Dry eye is a variation of the lacrimal functional unit (LFU), which includes the tear and meibomian glands, the ocular surface (cornea and conjunctiva), the eyelids and sensory and motor nerves. The LFU determines the characteristics of the tear film and preserves its integrity and corneal transparency and the quality of the images projected to the retina.(3) When direct or disease-derived damage occurs to LFU components, there is a risk of tear film destabilization that may manifest itself as dry eye. The epithelium will therefore be dry, the mucin will not be fixed, and the aqueous layer will not properly form on the affected corneal surface.(4) Damage to the ocular surface triggers the activation of sensory nerves, which results in the perception of symptoms, such as eye burning, foreign body sensation, itching, blurred vision, decreased vision, dryness, photophobia, eye fatigue and red eye.(5)

Menopause is one of the most common causes of dry eye.(6) Decreased sex hormones (estrogen and progesterone) cause alterations in the surface of the epithelium and alterations in secretions of the lacrimal gland and meibomian glands. Treatment with systemic or local androgen showed promising results in improving symptoms.(7) The administration of some oral drugs may aggravate or cause dry eye disease (DED). Tear hyposecretion disappears shortly after the cessation of medication. The main drugs that cause problems of dry eyes are anxiolytics, antidepressants, antihistamines, antihypertensives, diuretics, bronchodilators and strong analgesics.(8)

Artificial tears are a topically administered pharmaceutical product formulated to relieve the symptomatology of dry eye and supplement natural tears. These products should contain a high water content and possess physicochemical characteristics that are similar to natural tears, including osmolarity, pH, viscosity and surface tension.(9) Among the many artificial tear components, mucopolysaccharides stand out. These components are polysaccharides with viscoelastic properties, and the viscosity varies depending on the stress to which they are subjected. At rest, the viscosity is high, but the viscosity decreases. This property of mucopolysaccharides improves blurred vision compared to cellulose polymers. Hyaluronic acid, at concentrations of 0.1%, 0.15% and 0.18%, is the main mucopolysaccharide used. Increasing the concentration decreases the surface tension and increases contact with the ocular surface.(10)

Hyaluronic acid was recently crosslinked and efficacy was improved(11) versus non-crosslinked hyaluronic acid (CHA). This kind of artificial tears has been mixed with coenzyme Q10 and vitamin E. Due to the reticulated structure of hyaluronic acid, a lubricating liquid matrix is formed on the ocular surface. This matrix includes molecules of coenzyme Q10 and vitamin E, which enhance their antioxidant effect. Coenzyme Q10 also provides a source of energy and protection against oxidative stress to cells on the ocular surface, which facilitates repair of the tissue damage caused by dry eyes.(12)

The purpose of this study is to test non-inferiority of a lower total daily dose of crosslinked hyaluronic acid (CLHA) to a higher total daily dose of carmellose eye drop in menopause patients receiving antidepressant treatments. Efficacy based on posology is also compared.

Methods

Design

This prospective, double-blind, single-center and longitudinal study was performed between October 2018 and June 2019 at the facilities of the School of Pharmacy (Optics and Optometry department) of the University of Seville. The study was performed in accordance with the Ethical Committee Board of Andalusia and conducted according to the Declaration of Helsinki.

Subjects

Sixty female patients were enrolled in this study. All subjects read, understood and signed an inform consent. The following inclusion criteria were used: (1) women in menopause or the postmenopausal period; (2) active antidepressant or anxiolytics treatment; and (3) ocular surface disease index (OSDI) punctuation above 13 points. The following exclusion criteria were used: (1) soft or rigid gas-permeable contact lens use; (2) eyedrop use one month before the first instillation; (3) any previous eye surgery; (4) inability to understand informed consent; and (5) inability to comply with the proposed follow-up. Sixty-three of the total 78 patients met the inclusion and exclusion criteria. Three of the patients were excluded for noncompliance with the installation guidelines.

Materials

An eye slit lamp test was utilized to study the tear, and fluorescein stripes (Bio Glo ContaCare Ophthalmics & Diagnostics, Gujarat, India) soaked with saline solution were used for the breakup time test (TBUT). Tears were analyzed employing the cobalt blue filter of the slit lamp. Schirmer strip (Tear Flo, HUB Pharmaceutical, Plymouth, MI) was used to quantify tear volume. The Schirmer strip was located among the outer and middle third of the lower eyelid for five minutes, and the soaked length was measured in millimeters. The site, moment in time, and moisture conditions were the same for all patients examined. The patients also achieved the Ocular Surface Disease Index (OSDI) questionnaire throughout the first appointment and a questionnaire about their personal information, contact lenses type and wearing time.

Tear A eyedrops (VisuXL®, VISUfarma B.V ®, Amsterdam, The Netherlands) were formulated with 100 mg crosslinked hyaluronic acid (CLHA) sodium salt, 100 mg of coenzyme Q10 (CQ10) and 500 mg of vitamin E

TPGS (D-α-tocopherol polyethylene glycol succinate). The vitamin is a solubilizing agent for the CQ10 lipids. All of the components were dissolved in an isotonic buffered solution of 100 ml. The package was a 10-ml multidose bottle. Control tear B (Xailing Fresh ®, VISUfarma B.V ®, Amsterdam, The Netherlands) was formulated with 500 mg carmellose sodium in an isotonic buffered solution of 100 ml. The package contained 30 single 0.4-ml doses. The doses were packaged for daily use, and the eyedrops could not be used 12 hours after the dose dispenser was opened. These formulations were preservative-free lubricants.

Procedure

The study design comprised three phases. Potential patients were identified, and their inclusion or exclusion was evaluated in the first phase. Patients were recruited during prescription dispensing in the pharmacy office, and participation in the study was offered to people receiving tricyclic antidepressants (amitriptyline) or benzodiazepines anxiolytics (diazepam or lorazepam). These patients underwent an OSDI (Ocular Surface Disease Index) test to evaluate their fitness for inclusion in the study. Tear measurements were performed prior to treatment in the second phase. All patients in the study avoided the use of artificial tears or eye drops for one month. After this period, patients were given instructions on the proper instillation technique for artificial tears. We examined the selected patients with Schirmer I, tear break up time (TBUT) and the ocular surface disease index (OSDI) at the first visit. The amount of tears was measured by a Schirmer test, and the quality was measured using a TBUT test with fluorescein and blue light. Corneal staining was explored through the TBUT and was negative in all cases. These tests were performed in a blinded manner. Patients were given sufficient artificial tears for two months and the patient instruction sheet, which indicated the dose, during this same visit. Patients who received carmellose instilled the drops five times daily, and patients who received CLHA tears instilled the drops twice daily. The third phase consisted of tear measurements at the end of the treatment. After two months, the patients were checked again, and the OSDI test, Schirmer and TBUT were performed. The results of this second consultation were recorded in another document than the previous results to avoid subjective bias of the researcher. These second measurements were performed without knowledge of the type of tear received. Patients were associated with a number to preserve anonymity. Two different records were maintained: one record contained the results of the tests, and the other included the type of tears that were randomly assigned. The data of both records were crossed after study completion to obtain the results.

Statistical analysis

The data were analyzed using the SPSS 25 package for Windows (SPSS Science, Chicago, IL). The normality of the variables was verified using the Shapiro-Wilk test. A descriptive data analysis technique was developed and showed the count and proportion in each category of the qualitative variables and the means and SD. Student's t-test was performed between the two groups, and the effect size was calculated with D of Cohen(13) formula. All statistical tests were performed with a 95% confidence level ($p < 0.05$).

Results

The mean age of the patients was 63.25 ± 9.13 (45 to 85) years. Artificial tear A group had an OSDI of 30.45 ± 10.02 (13.75 to 47.92) score points prior to treatment. The Schirmer test was 12.70 ± 10.91 (1 to 35) mm, and the TBUT test was 4.03 ± 1.24 (2 to 8) s. Artificial tear B group reported an OSDI test of 31.20 ± 8.17 (17.50 to 46.29) score points, which was no significantly different from the values for group A (P = .75). The Schirmer test was 11.73 ± 9.71 (1 to 35) millimeters (mm) and was not significantly different from the results of group A (P = .71), and the breakup time (TBUT) test was 4.27 ± 1.46 (1 to 7) seconds (s) and was not significantly different from the results of group A (P = .50).

Ocular Surface Disease Index (OSDI)

In relation to OSDI, the artificial tear A group obtained 14.12 ± 7.47 (2.50 to 29.65) score points (t = 11.74, P < .01). This supposes a large effect size of 1.84. The OSDI decreased to 16.33 ± 7.61 (13.49 to 19.18, 95% confidence interval) score points. The artificial tear B group obtained 19.46 ± 10.03 (2.80 to 38.50) score points (t = 7.59, P < .01). This supposes a large effect size of 1.28. The OSDI decreased to 11.74 ± 8.46 (8.57 to 14.90, 95% confidence interval) score points. Differences are reported in Figure 1. Post-treatment comparisons between the artificial tears revealed that group A obtained better results with a difference of 5.34 ± 2.28 (0.76 to 9.91, 95% confidence interval) score points (t = 2.33, P < .05).

Schirmer test

In relation to the measured tear volume, the artificial tear A group obtained 13.77 ± 7.78 (2 to 35) score points (t = 0.88, P > .05). This supposes a small effect size of 0.11. Schirmer increased only 1.06 ± 6.62 (1.40 to 3.5, 95% confidence interval) mm. The artificial tear B group obtained 14.20 ± 8.62 (5 to 35) score points (t = 2.92, P < .01). This supposes a small effect size of 0.26. Schirmer increased 2.46 ± 4.62 (0.74 to 4.17, 95% confidence interval) mm. Differences are reported in Figure 2. Post-treatment comparison between the artificial tears revealed no significant differences between groups (t = 0.20, P = .83), with a difference of 0.43 ± 2.12 (-3.81 to 4.68, 95% confidence interval) mm.

Tear breakup time test (TBUT)

In relation to the tear quality, the artificial tear A group obtained 8.30 ± 2.08 (4 to 12) seconds (t = 15.50, P < .01). This supposes a large effect size of 2.49. The TBUT increased by 4.26 ± 1.50 (3.70 to 4.80, 95% confidence interval) seconds. The artificial tear B group obtained 7.23 ± 2.40 (4 to 12) seconds (t = 8.79, P < .01). This supposes a large effect size of 1.49. The TBUT increased by 2.96 ± 1.84 (2.27 to 3.65, 95% confidence interval) seconds. Differences are reported in Figure 3. Post-treatment comparisons between the artificial tears revealed that group A obtained better results with a difference of 1.06 ± 0.58 (0.10 to 2.23, 95% confidence interval) score points (t = 1.83, P < .05).

Discussion

This prospective, double-blind, single-center study compared the efficacy of crosslinked hyaluronic acid with coenzyme Q10 and vitamin E against carmellose eyedrops in dry eye patients under antidepressant or anxiolytics treatment during a two-month management period. Lower total daily dose of CLHA obtained same results in some clinical signs and symptoms compared to higher total daily dose carmellose eyedrops.

The use of hyaluronic acid in patients with moderate to severe dry eye syndrome had been widely studied (14–16), and it significantly improved symptoms, such as burning, redness, photophobia, and foreign body sensation. CLHA was used previously to analyze the ocular surface properties in dogs(17–19) with keratoconjunctivitis sicca, and they demonstrated the efficacy of CLHA in reducing the clinical signs associated with dry eye. Fallacara et al.(20) reported the in vitro re-epithelialization assessment ability of two different preparations containing CLHA with urea. They demonstrated, for the first time, hopeful results for the use of CLHA eyedrops for the management of dry eye symptoms and corneal injuries in human eyes. To our knowledge, the first in vivo study in humans was performed by Cagini et al. (11) who compared the stability of the tear film after the instillation of eye drops containing HA or CLHA in patients with Sjögren's dry eye. Their methodology studied tear stability only during the first sixty minutes after instillation and reported that CLHA eyedrops obtained better tear stability than uncrosslinked HA. These results are consistent with the TBUT results of our study.

All of the patients in our study experienced less dry eye symptoms after treatment and obtained better results on OSDI, TBUT and Schirmer I tests. The amelioration was larger in group A, who received cross-linked hyaluronic acid, compared to group B, who received carmellose, even with the higher total daily dose used in group B. Tear A OSDI decreased 16.33 ± 7.61 score points while Tear B OSDI decreased 11.74 ± 8.46, this supposed a statistically significant difference between both groups of 4.59 ± 2.07 score points ($t = 2.21$, $P < .05$). Tear A TBUT increased 4.26 ± 1.50 seconds while Tear B TBUT increased 2.96 ± 1.84 seconds, this supposed a statistically significant difference between both groups of 1.30 ± 0.43 seconds ($t = 2.98$, $P < .01$). Tear A Schirmer increased 1.06 ± 6.62 mm while Tear B Schirmer increased 2.46 ± 4.62 mm, this supposed a non-statistically significant difference between both groups of 1.40 ± 1.47 mm ($t = -.95$, $P = .34$). Cross-linked hyaluronic acid contributes to a better lubrication effect than carmellose due to the reticulated structure, which forms a liquid matrix on the ocular surface. This matrix includes coenzyme Q10 molecules and vitamin E, which exert antioxidant effects that contribute to the epithelial ocular surface repair. Only two drops of artificial tears with

cross-linked hyaluronic acid with coenzyme Q10 and vitamin E is sufficient to ameliorate postsurgical recuperation after cataracts surgery.(21)

Crosslinked hyaluronic acid eyedrops with coenzyme Q10 and vitamin E are scarcely studied. Postorino et al (12) compared these artificial tears versus lineal hyaluronic acid, but these patients were not under pharmacological treatments that contributed to eye dryness, as in our study. Crosslinked and lineal hyaluronic acid tears were also used at the same total daily dose in Postorino's study, but we administered a higher total daily dose of carmellose compared to crosslinked hyaluronic acid. Despite the differences between both studies, crosslinked hyaluronic acid showed better efficacy in dry eye management. A recent review by Posarelli et al. (22) found that the current pharmacological trend is improving the properties of hyaluronic acid via crosslinking parts of the molecule to achieve better bioavailability and resistance to degradation. These studies conclude that CLHA as a tear supplement provides better ocular comfort than linear hyaluronic acid in dry eye disease, and it is the subject of growing interest and discussion.

Previous authors have similar results with crosslinked hyaluronic acid in dry eye disease against non-crosslinked hyaluronic acid or against other artificial tears such carmellose. However, among the strengths, this is, to best of our knowledge the first to report these findings in menopause women receiving antidepressant or anxiolytic treatment. Regarding the limitations, sample size could be higher and other variables, such osmolarity test could increase outcomes reliability.

Lower total daily dose of crosslinked hyaluronic acid eyedrops obtained similar efficacy results in terms of tear stability and subjective dry eye sensation than higher carmellose total daily dose. The CLHA group demonstrated that a lower total daily dose was sufficient to achieve better dry eye disease management compared to carmellose. This difference was due to the longer permanence time of the tears on the ocular surface of the crosslinked hyaluronic acid and the repairing effects of the antioxidants.

Author Disclosure Statement

The Authors declare that there is no conflict of interest

Funding Declaration

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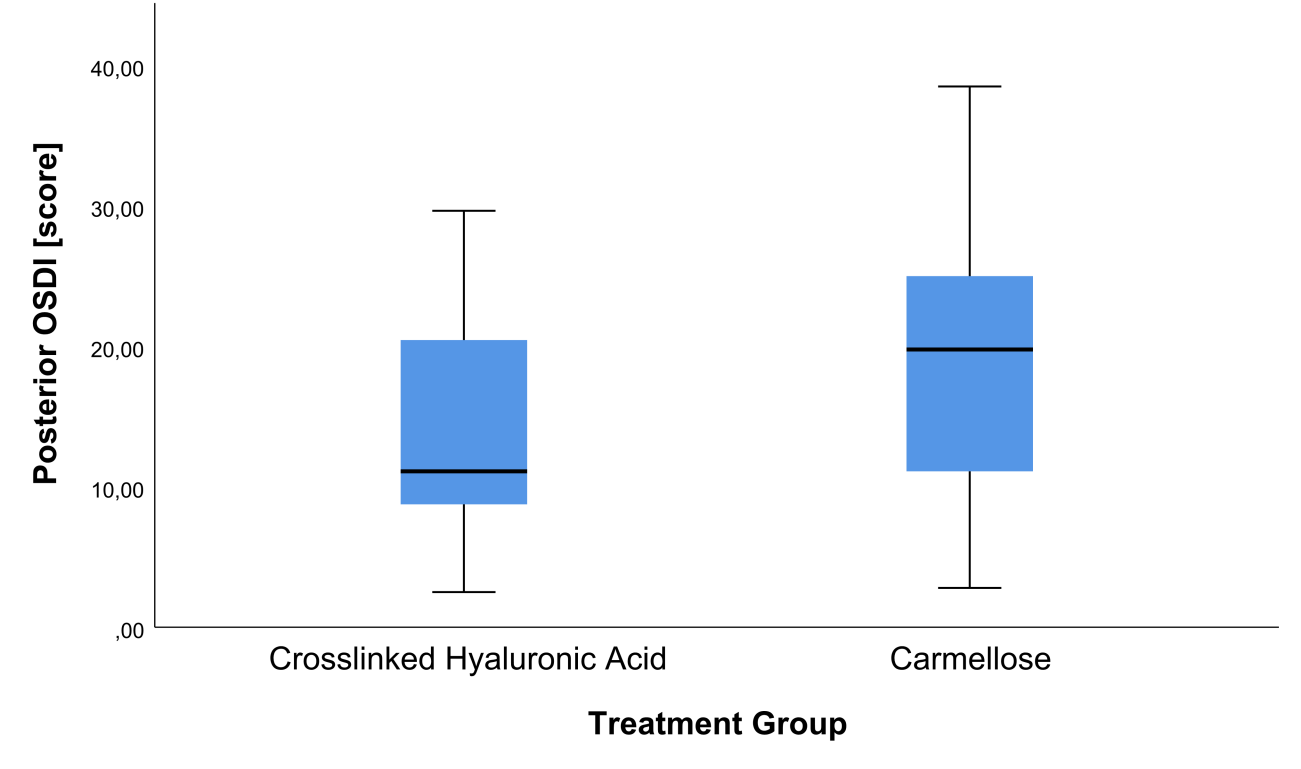
Figure legends

Figure 1. Subjective dry eye symptoms using the ocular surface disease index (OSDI). Comparative boxplots of crosslinked hyaluronic acid with coenzyme Q10 and vitamin E eyedrop versus carmellose eyedrops.

Figure 2. Tear volume using the Schirmer I test. Comparative boxplots of crosslinked hyaluronic acid with coenzyme Q10 and vitamin E eyedrop versus carmellose eyedrops.

Figure 3. Tear stability with breakup time (TBUT). Comparative boxplots of crosslinked hyaluronic acid with coenzyme Q10 and vitamin E eyedrop versus carmellose eyedrops.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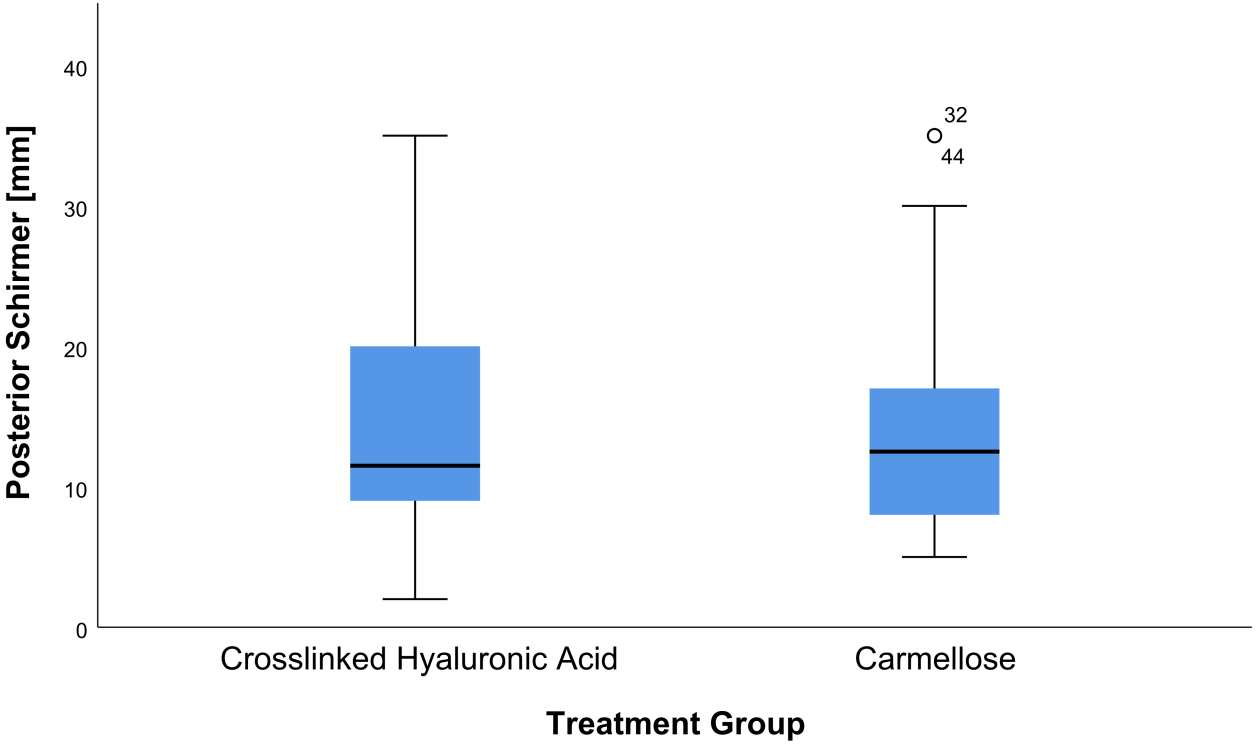
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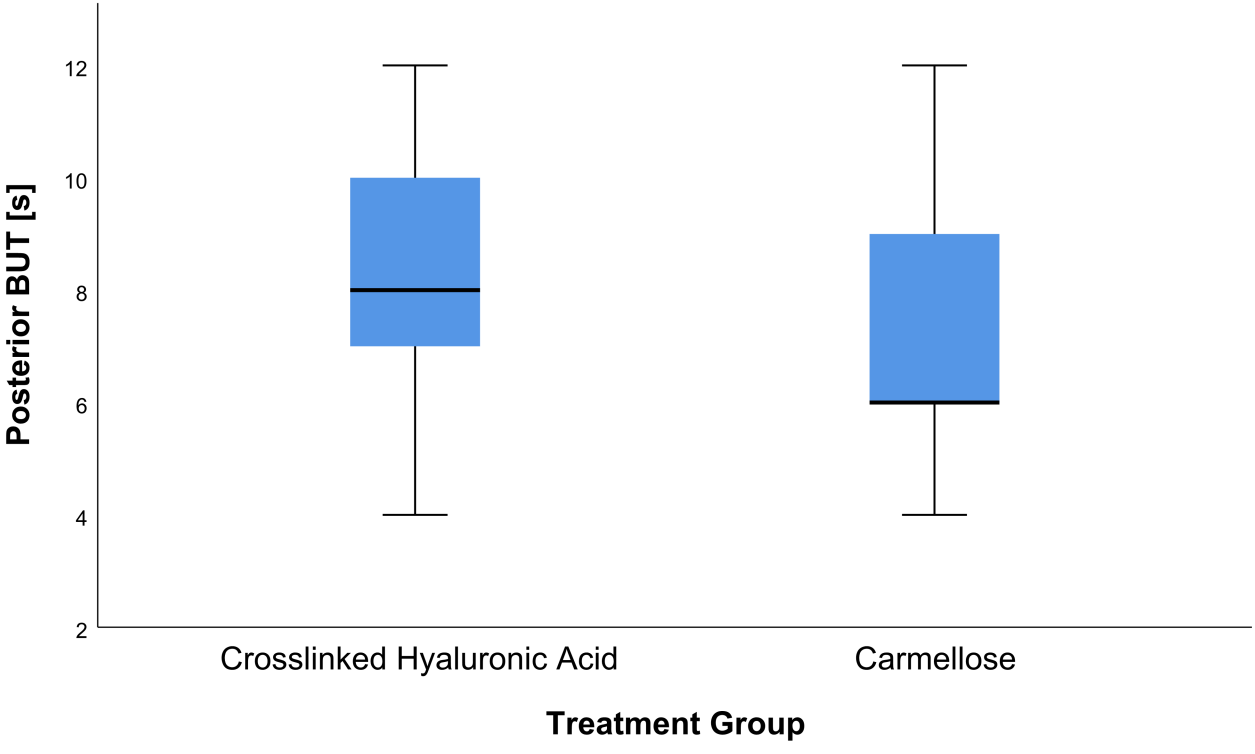
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