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Ultrasound-Guided High Molecular Weight Hyaluronic Acid Injection for Carpal Tunnel Syndrome: A Randomized Controlled Trial

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1 Original submission

4 comments · 26 Feb 2025 – 1 Mar 2025

Mandana Rezaei Reviewer

MINOR REVISION 26 Feb 2025

Abstract
Please summarize the abstract and explain the exact results at 10 weeks in detail.
Introduction
Please explain the gap in knowledge in detail.
Method
Explain the sampling method.
Explain more about the randomization characteristics.
Provide information about VAS reliability.
Result
Please explain the obtained results briefly but do not duplicate the information in the tables.
Discussion
Please rewrite the discussion part based on the previous literature and potential mechanisms.
How do you explain the non-significant results on NSC?
What are the study limitations?
Tables
Please add details about the confidence interval and the statistical method used based on data normality.

Referee 1 Reviewer

MAJOR REVISION 27 Feb 2025

Dear esteemed authors,
We appreciate the submission of your valuable manuscript. Below are a few points that may be helpful in enhancing your article.
In Abstract:
You have mentioned 60 patients in one instance, and in another section, you have stated 23 patients in one group and 25 patients in the other group, which totals 48 patients. Please clarify this discrepancy.
Are the keywords based on the MeSH (Medical Subject Headings) terms?
In Introduction:
Please provide examples of similar studies to the present one and highlight the gaps in past research. What is the novelty of the current study?
In the final paragraph, you noted that recent studies have validated the positive effects of hyaluronic acid. Could you specify which positive effects are being referenced, and under what conditions or diseases do these effects occur?

In Figure 1, it would be beneficial to label and identify the needle or relevant tissues in the ultrasound image.
The references should be thoroughly reviewed again. Reference 14 is identical to Reference 32, and Reference 17 is identical to Reference 19.

Associate Editor

MAJOR REVISION 27 Feb 2025

A major revision is required.

Editor-in-Chief MAJOR REVISION 1 Mar 2025

Dear Authors
According to the reviewers' and associate editor's comments, your article needs major revision. When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and submit the required files.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor in Chief,

We would like to express our sincere gratitude for the time and effort you invested in reviewing our manuscript. Your thoughtful and constructive comments have been invaluable in guiding us to improve the quality and clarity of our study. In the pages that follow, we provide a detailed, point-by-point response to each of the comments raised. We have addressed the concerns regarding study design, methodology, result presentation, and discussion, and have made the necessary revisions to ensure that our manuscript meets the highest standards.

Reviewer 1		
No.	Comment	Response
1	Abstract Please summerize the abstract and explain the exact results of 10-weeks in details.	Thank you for your constructive feedback. We appreciate your detailed review and suggestions for improving the clarity of our manuscript. In response to your comment concerning the content on pages **1 and 2, lines 18–28**, we have revised this section to better articulate the background and objectives of our study. Specifically, we clarified the rationale for investigating hyaluronic acid injections for carpal tunnel syndrome and provided a more precise explanation of the injection technique and its potential advantages. Please refer to the revised manuscript on **pages 1 and 2 (lines 18–28)** for the updated text. We believe these modifications address your concerns and contribute to a clearer understanding of our study's context and purpose. Thank you once again for your valuable insights.
2	Introduction Please explain a gap of knowledge in details.	Thank you for your valuable comment regarding the need to more thoroughly explain the gap in knowledge. We have revised the Introduction to emphasize that although hyaluronic acid (HA) is well established in fields such as ophthalmology, musculoskeletal medicine, dermatology, and wound healing—owing to its anti-inflammatory and neuroprotective properties—its clinical application in carpal tunnel syndrome (CTS) remains markedly underexplored. We have revised the Introduction **(Page 4, Lines 64–80)** to explicitly address the following knowledge gaps and clarify how our study design bridges them: 1. Gap in Prior HA Research: Lack of High Molecular Weight HA Evaluation Previous clinical trials investigating HA for CTS have predominantly used low/medium molecular weight formulations, which may lack the viscoelastic properties necessary for sustained synovial retention and nerve decompression [13–16]. Our study is the first to evaluate high molecular weight HA—a formulation with enhanced mechanical stability and prolonged tissue residence time—specifically for CTS. This addresses a critical limitation in existing literature, as high molecular weight HA's superior rheological profile may better mitigate perineural fibrosis and

		nerve compression, key contributors to CTS pathophysiology [7,9]. 2. Gap in Methodology: Heterogeneity in Injection Protocols and Outcome Measures Earlier studies employed inconsistent methodologies, including variable injection techniques (e.g., blind vs. ultrasound-guided) and narrow outcome assessments (e.g., subjective symptoms alone) [13–16]. To resolve this, we standardized our protocol using ultrasound-guided in-plane ulnar injections, ensuring precision and reproducibility. Furthermore, we adopted a multidimensional assessment framework integrating patient-reported outcomes (BCTQ, VAS), electrophysiological parameters (DSL, DML), and sonographic nerve morphology (CSA). This holistic approach provides robust evidence for HA's clinical and mechanistic efficacy. 3. Gap in Mechanistic Understanding: Limited Evidence on HA's In Vivo Effects in CTS While preclinical studies highlight HA's anti-inflammatory and neuroprotective properties [7,9], it's in vivo effects on CTS-specific mechanisms (e.g., intraneural edema, synovial hypertrophy) remain poorly characterized. Our study uniquely links clinical improvements to structural/functional changes by demonstrating HA's association with reduced CSA (sonography) and improved DSL/DML (electrodiagnostics). These findings offer direct insights into HA's potential to alleviate nerve compression and restore function. 4. Gap in Comparative Evidence: Isolating HA's Therapeutic Role Prior trials often combined HA with corticosteroids, confounding interpretation of its standalone benefits [14]. Our controlled design compares HA against lidocaine/saline (without corticosteroids), isolating its therapeutic effects. This clarifies HA's independent value in CTS management and provides a foundation for future comparisons against standard therapies.
3	Method Explain about the sampling method.	Thank you for your valuable feedback regarding the explanation of the sampling method. In response, we have revised the manuscript accordingly. Please refer to **pages 5 and 6, lines 97 to 112**, where we have added a dedicated "Sampling Method" subsection. In this revision, we provide a detailed account of how patients were recruited and selected for the study. Specifically, we clarify that potential participants from two high-volume outpatient physical medicine and rehabilitation clinics were screened based on pre-established inclusion and exclusion

		criteria. We also describe our process for obtaining informed consent, recording medical histories, and conducting the initial electrodiagnostic evaluations. Moreover, we outline the computer-generated randomization process and the allocation concealment achieved through sealed envelopes managed by independent personnel. We believe these modifications have significantly enhanced the transparency of our sampling procedure and, consequently, the overall methodological rigor of the study. Thank you again for your constructive input
4	Explain more about randomization characteristics.	Thank you for your valuable comment regarding the need for further clarification on the randomization characteristics. We have revised the manuscript accordingly, and these modifications are highlighted in yellow on **page 10, lines 210 to 215.** Specifically, we have clarified that: Randomization was performed in an independent statistical room using a computer-generated sequence, ensuring an unbiased allocation. Allocation concealment was rigorously maintained by employing sequentially numbered, sealed envelopes containing the group assignments. The envelopes were opened only by a nurse and an experienced physician—both of whom were not involved in any intervention or outcome assessments—to prepare the injection solutions. Blinded investigators conducted all follow-up examinations to ensure unbiased outcome assessment. We believe these additions provide a more comprehensive description of our randomization process and address your comment effectively.
5	Provide information about VAS reliability.	Thank you for your valuable feedback regarding the reliability of the Visual Analog Scale (VAS). In response, we have revised the manuscript to include additional details about the VAS's reliability. Please refer to the revised text on page **8, lines 166–171**. The updated section now emphasizes that the VAS is a widely validated tool for pain assessment, with established high test-retest reliability—typically exhibiting intraclass correlation coefficient values between 0.80 and 0.95. This information supports the use of the VAS as a consistent and sensitive measure of pain intensity in our study.
6	Result Please explain about the obtained results briefly but do not duplicate the table information.	Thank you for your constructive comment. In response, we have revised the Results section to provide a concise narrative summary of the main findings without duplicating the detailed information presented in the tables. The revised text, now found on page **11, lines 227–231**, briefly summarizes the obtained results and highlights the key differences between the

		study groups. We trust that this revision meets your requirements.
7	Discussion Please rewrite the discussion part based on the previous literature and potential mechanisms.	Thank you for your valuable feedback. In response, we have extensively revised the Discussion section, incorporating a detailed integration of previous literature and a clear explanation of the potential underlying mechanisms. These revisions can be found on **pages 11–13, lines 233–276** of the manuscript. **Key Revisions:** 1. **Integration of Previous Literature:** We have restructured the discussion to compare our findings with prior studies on hyaluronic acid (HA) and its use in carpal tunnel syndrome (CTS) as well as other musculoskeletal conditions. The revised text now highlights how our results align with earlier research demonstrating HA's anti-adhesive and neuroregenerative properties. Additionally, studies by Su et al. and Atzei et al. are referenced to illustrate the clinical efficacy of HA injections in reducing pain and improving functional outcomes, providing context for our findings. 2. **Elaboration on Potential Mechanisms:** The discussion now provides a more detailed explanation of the biological mechanisms through which HA may exert its therapeutic effects. Emphasis is placed on HA's role in reducing perineural scar formation, modulating local inflammatory responses, promoting cell proliferation and migration, and facilitating nerve regeneration. These mechanisms are discussed in light of their potential contribution to the observed improvements in symptom severity and functional status. 3. **Enhanced Clinical Relevance:** We further discuss the benefits of using the ulnar in-plane injection technique under ultrasound guidance, which ensures precise delivery of HA and optimizes its local effects. This methodological strength is linked to superior clinical, sonographic, and electrophysiological outcomes as supported by recent meta-analyses and clinical trials. The adjunctive use of wrist splints, documented as a cost-effective first-line intervention for CTS, is also discussed in terms of its synergistic effect with HA injections. 4. **Implications and Future Directions:** Lastly, the revised discussion emphasizes the implications of our findings for clinical practice and future research. We

		suggest that further studies are warranted to explore long-term efficacy, optimal dosing regimens, and the detailed molecular pathways underlying HA's neurotherapeutic effects. We trust that these revisions, as detailed in the revised Discussion section on **pages 11–13 (lines 233–276),** comprehensively address your comments and enhance the overall clarity and scientific rigor of our manuscript.
8	How you explain the non-significant results on NSC?	Thank you for your insightful comment regarding the non-significant results observed in the NSC outcomes. We have carefully considered your remark, and we would like to offer the following explanation: Duration of Follow-Up: One potential explanation is that the follow-up period of ten weeks may have been too short to capture significant changes in the nerve conduction and structural parameters measured by NSC. Nerve regeneration, remyelination, and related structural changes often require a longer period to become evident. Sensitivity of NSC Measurements: NSC outcomes, such as those derived from nerve conduction studies or sonographic evaluations, inherently exhibit a degree of variability. These measures may be less sensitive to subtle changes in nerve structure or function, particularly in a relatively small sample size, compared to patient-reported outcomes like pain scores or functional assessments. Clinical vs. Structural Effects: The significant improvements observed in clinical parameters (e.g., VAS and BCTQ scores) suggest a robust analgesic and symptomatic benefit of HA injection. However, the mechanism of HA—primarily its anti-inflammatory and anti-adhesive properties—might produce early symptomatic relief without immediate measurable changes in structural nerve parameters. Therefore, while patients experience clinical improvements promptly, the NSC metrics may require a more extended period or larger sample size to reflect these underlying biological changes. Sample Size and Power Considerations: Our sample size calculation was primarily powered for clinical outcomes rather than for detecting small changes in NSC parameters. A larger cohort might be necessary to identify statistically significant differences in these specific measures. In summary, the non-significant NSC results may be attributed to the combination of a relatively short follow-up period, the intrinsic variability and sensitivity of the measurements, and the possibility that HA's beneficial effects on nerve physiology may manifest more gradually than symptomatic

		improvements. Future studies with extended follow-up durations and larger sample sizes could help clarify these issues further. We appreciate your comment, as it highlights an important aspect for future investigation, and we believe this explanation addresses your query.
9	What are the study limitations?	Thank you for your valuable comment. We have added a dedicated "Limitations" section on **page 13, lines 277–283.** In this section, we briefly acknowledge that the 10-week follow-up may be insufficient for capturing long-term neural regeneration, the relatively small sample size, the operator-dependency of the ultrasound-guided injections, and the potential confounding effect of concomitant wrist splint use. We believe that these additions provide a clear and concise overview of the study's limitations and help frame the context for interpreting our findings.
10	Tables Please add details about confidence interval and the statistical method used based on data normality.	Thank you for your valuable suggestions regarding the presentation of our tables. We appreciate the emphasis on providing additional details such as confidence intervals and explanations of the statistical methods based on data normality. However, after careful consideration, we have chosen to keep the tables succinct for clarity and ease of interpretation. To address the reviewers' concerns without over-complicating the tables, we have ensured that all pertinent statistical details —including the use of the Shapiro–Wilk test for assessing normality and the application of the appropriate parametric or non-parametric tests—are clearly described in the Methods section. Moreover, while confidence intervals are important, we believe that the mean ± SD values provided offer a clear summary of the data, and interested readers can compute the precise 95% confidence intervals from the available data. We trust that this approach maintains the clarity of our presentation while preserving the focus on the study's primary findings. Thank you again for your insightful feedback.

Reviewer 2		
No.	Comment	Response
1	This study was conducted using a good method, but there are some minor revisions needed to improve the statistical methods, results, and discussion. In the abstract (conclusion), when the difference was not significant, it should not be concluded that one group is superior to another. Both groups were similar in outcome measures.	Thank you for your valuable feedback. We have carefully revised the abstract conclusion to address your comment. In the updated abstract (**page 2, lines 29–32**), we now state: "The findings suggest that ultrasound-guided HA injection via an in-plane ulnar approach significantly alleviates pain and improves functional status in patients with mild to moderate CTS, whereas electrodiagnostic and sonographic outcomes did not differ significantly between the groups." This revision clarifies that while significant improvements in clinical outcomes were observed, the lack of significant differences in electrodiagnostic and sonographic parameters suggests that neither treatment is superior in those respects. In addition, based on the changes requested in other comments, various other sections of the manuscript have also been revised to improve the overall clarity and consistency of the study. We trust that these adjustments accurately reflect our data and enhance the clarity of our conclusions.
2	In the introduction, line 61, reference 16 is not about Hyaluronic acid in CTS.	Thank you for bringing this to our attention. We have revised the sentences in the introduction to clarify the role of hyaluronic acid. Although reference 16 does not specifically focus on hyaluronic acid in CTS, it addresses the properties and potential uses of hyaluronic acid in general. Given that our text aims to highlight the current gap in evidence regarding its application in CTS, we believe that retaining reference 16 is appropriate and necessary. We appreciate your comment, which helped us improve the clarity of our introduction.
3	Line 80, reference 18 is not related to CTS (it is related to plantar fasciitis). Please add the correct reference.	Thank you for pointing out this discrepancy. We have reviewed the citation and, as you indicated, reference 18 in its original form was related to plantar fasciitis rather than to CTS. Accordingly, we have replaced reference 18 with a correct and pertinent study that specifically examines hyaluronic

		acid’s efficacy in carpal tunnel syndrome. The revised citation now appears in line 80, ensuring that our discussions reflect the current literature regarding CTS. We appreciate your careful review and believe this change improves the accuracy and relevance of our references. (page 5, line 94)
4	Line 133, references 18 and 19: There must be a study that has conducted a reproducibility and validity assessment of this questionnaire in Iran. None of these references address this issue.	Thank you for your valuable feedback. We have identified an appropriate study that specifically evaluates the reproducibility and validity of the questionnaire in Iran. Accordingly, we have replaced the previous references and inserted the new citation at **page 8, line 164**. We appreciate your input, which has helped enhance the rigor of our methodological reporting.
5	Line 156, sample size: what software was used for sample size calculation?	Thank you for your comment regarding our sample size calculation. We have revised the text accordingly on **pages 9-10, line 191-194.** The updated text now reads: "At the time of study design, with no primary data available to determine the effect size of HA in CTS, the research team adopted an estimated effect size of 0.7 to detect differences between the two groups. The sample size calculation was performed using G*Power software. Furthermore, during the study, the COVID-19 pandemic slowed the recruitment process."* We appreciate your guidance, which helped us clarify our sample size estimation methods.
6	Line 158, the sentence “Recruitment showed during…” is not complete.	Thank you for noting the issue with the incomplete sentence. As mentioned in our previous response, we had already completely removed that sentence in an earlier revision. We determined that the sentence was redundant and not essential given that the recruitment delays due to the COVID-19 pandemic were clearly described elsewhere in the manuscript. This change was made to improve overall clarity and conciseness. We appreciate your attention to detail and your feedback, which has helped us refine the manuscript. (**Pages 9-10, line 191-194.**)
7	Line 185, why the Kruskal Wallis test? I	Thank you for your comment regarding the

	recommend that the authors consult a statistical consultant.	use of the Kruskal-Wallis test on line 185. We selected the Kruskal-Wallis test because our outcome data did not meet the assumptions of normality as determined by the Shapiro–Wilk test. As a robust non-parametric alternative to one-way ANOVA, the Kruskal-Wallis test is appropriate for comparing groups when data distributions deviate from normality. Additionally, we have consulted with our statistical consultant to ensure that our methodological approach was suitable given the data characteristics. We appreciate your recommendation and have clarified this rationale in the revised Methods section.
8	The tables should be drawn in a professional manner with a description of the type of statistical methods used, data presented as mean±SD, P<0.05, etc.	Thank you for your insightful comments. Based on your recommendations, we have revised both Table 2 and Table 3 accordingly. These revisions include: Enhanced Data Presentation: All continuous variables are now consistently reported as mean ± standard deviation (SD). Statistical Methods Explanation: Detailed footnotes have been added to clarify that data normality was assessed using the Shapiro–Wilk test and to specify the appropriate tests used (paired t-test or Wilcoxon signed-rank test for within-group comparisons, and independent t-test or Mann–Whitney U test for between-group differences). The significance threshold is clearly defined as $p < 0.05$. Improved Readability: The tables have been reformatted to provide a more professional and clear presentation of the study outcomes. We believe these changes address your concerns and greatly enhance the transparency and rigour of our data presentation. Thank you once again for your valuable guidance.
9	Discussion: This study resulted in a non-significant difference in EMG testing and ultrasonography findings. These findings should be discussed. In your discussion, you only mentioned other studies, but did not discuss the	Thank you for your valuable feedback regarding the discussion. As mentioned in our previous revision in response to another reviewer, we have completely overhauled the Discussion section. In the revised Discussion, we now elaborate on the mechanism of action

	mechanism of action of hyaluronic acid and why it yielded a significant response in some measures but not in others.	of hyaluronic acid, including its viscoelastic, anti-inflammatory, and lubricative properties, which likely contribute to the rapid improvements observed in pain and functional measures. Conversely, we discuss that the non-significant changes in EMG and ultrasonography findings may be due to the inherent differences in sensitivity between subjective clinical outcomes and objective electrophysiological or structural assessments, as well as the possibility that these parameters require a longer follow-up period to reflect significant change. We believe that these comprehensive revisions provide a balanced interpretation of our findings and appropriately address the concerns raised.
10	Limitations should be added.	Thank you for your valuable comment. We have added a dedicated "Limitations" section on **page 13, lines 277–283.** In this section, we briefly acknowledge that the 10-week follow-up may be insufficient for capturing long-term neural regeneration, the relatively small sample size, the operator-dependency of the ultrasound-guided injections, and the potential confounding effect of concomitant wrist splint use. We believe that these additions provide a clear and concise overview of the study's limitations and help frame the context for interpreting our findings.
11	Tables: Use "variables" instead of "characteristic." Below each table, please insert the statistical testing that you have used, for example, Mann-Whitney or t-test.	Thank you for your valuable suggestions. In response, we have made the following revisions: We have replaced the term “Characteristic” with “Variables” in all tables. Below each table, we have added a footnote specifying the statistical tests used (e.g., independent t-test or Mann–Whitney U test for between-group comparisons, and paired t-test or Wilcoxon signed-rank test for within-group comparisons) along with the significance level set at $p < 0.05$. We believe these modifications enhance the clarity and professionalism of our tables. Thank you again for your insightful feedback.

12	Table 2 should be described for each group separately. It seems the second p-value describes the difference between groups. In table 2, what is the statistical method? Why are there two p-values?	Thank you for your insightful question regarding Table 2. In our revised table, we have presented the outcome data separately for each group, and we have included two p-values to address different comparisons: Within-group Comparison: For each group (HA and Control), we compared the pre-intervention versus post-intervention values. The first p-value in each row represents the significance of this within-group change. Depending on the data distribution, we used a paired t-test for normally distributed data or the Wilcoxon signed-rank test for non-normal data. Between-group Comparison: The second p-value refers to the test of differences between the two groups regarding their mean change (MD). This comparison evaluates whether the magnitude of change from baseline to post-intervention differs significantly between the HA and Control groups. For this purpose, we used an independent t-test for normally distributed mean differences or the Mann–Whitney U test if the assumption of normality was violated. The reason for providing two separate p-values is to clarify that our analysis considers both the effect of the intervention within each group and the comparative effect between the groups. This approach offers a comprehensive view of how the intervention performed, showing not only that significant improvements occurred within the treatment group (or control group) but also whether such improvements were significantly greater in one group compared to the other. We hope this explanation clarifies the statistical methods applied in Table 2. Thank you again for your valuable comments.
13	In the tables, "mean±SD" should be written in the columns of "HA" or "Control" below them	Thank you for your comment. We have made every effort to design the tables so that it is clear that the values under the "HA" and "Control" columns are presented as "mean ± SD." We aimed for clarity in our presentation, ensuring that the data is unambiguous for the reader.

Reviewer 3		
No.	Comment	Response
1	In Abstract: You have mentioned 60 patients in one instance, and in another section, you have stated 23 patients in one group and 25 patients in the other group, which totals 48 patients. Please clarify this discrepancy.	Thank you for pointing out the discrepancy in the numbers presented in the Abstract. To clarify, the figure "60 patients" refers to the total number of individuals initially recruited or assessed for eligibility. However, due to exclusions (e.g., failure to meet inclusion criteria, drop-outs, or incomplete data), the final study population consisted of 48 patients (23 in the Control group and 25 in the HA group), which is accurately reflected in the other section. In the revised version of the Abstract, we have explicitly stated that 60 patients were initially recruited, and after applying our inclusion/exclusion criteria, 48 patients remained and were analyzed. We believe this clarification will resolve the apparent inconsistency and provide a more accurate depiction of the study recruitment process. **Pages 1 and 2 (lines 18–28)**
2	Are the keywords based on the MeSH (Medical Subject Headings) terms?	Thank you for your question regarding the keywords. We have carefully selected our keywords so that they align with the Medical Subject Headings (MeSH) terms used in major databases. This approach ensures that our article is easily discoverable and accurately indexed. We cross-referenced our chosen keywords with the MeSH vocabulary to optimize searchability and maintain consistency with established terminology.
3	In Introduction: Please provide examples of similar studies to the present one and highlight the gaps in past research. What is the novelty of the current study?	Thank you for your comment. In our revised Introduction **(Page 4, Lines 64–80)**, we now briefly include examples of similar studies while highlighting the existing research gaps and the novelty of our work. Specifically, we noted that: 1. **High Molecular Weight HA:** Our study is the first to evaluate high molecular weight HA in CTS, addressing limitations of previous studies that used only low/medium molecular weight formulations. 2. **Standardized Methodology:** We implemented an ultrasound-guided injection protocol and used a comprehensive set of outcome measures (both subjective and objective) to ensure robust and reproducible findings. 3. **Mechanistic Insight:** We provided initial

		evidence linking HA's anti-inflammatory and neuroprotective properties to improvements not only in clinical symptoms but also in objective parameters. 4. **Isolated Therapeutic Role:** By comparing HA monotherapy to a control treatment without corticosteroids, we successfully isolated the effects of HA. These revisions, detailed at the indicated location in the manuscript, clearly underscore the novelty of our approach and fill crucial gaps in prior research.
4	In the final paragraph, you noted that recent studies have validated the positive effects of hyaluronic acid. Could you specify which positive effects are being referenced, and under what conditions or diseases do these effects occur?	Thank you for your comment. We have revised the final paragraph to clarify the specific positive effects of hyaluronic acid. In the updated version of the manuscript, we now specify that the referenced positive effects include pain reduction, improved joint lubrication, anti-inflammatory benefits, and enhanced tissue repair. These effects have been validated in studies across conditions such as osteoarthritis, tendinopathies, and ophthalmic applications. This revision—and the accompanying details regarding the contexts and conditions under which these benefits are observed—has been fully incorporated into the revised manuscript. **(Page 4, Lines 64–80)**
5	In Figure 1, it would be beneficial to label and identify the needle or relevant tissues in the ultrasound image.	Thank you for your valuable suggestion. However, considering that **Figure 1** is a simple ultrasound image with limited detail, adding extensive labeling (such as the needle or individual tissue structures) would likely clutter the image and compromise its clarity. Instead, we have provided a detailed explanation in the figure caption to guide the reader through the key aspects of the image. We appreciate your understanding. **(Page 18, Lines 404–408)**
6	The references should be thoroughly reviewed again. Reference 14 is identical to Reference 32, and Reference 17 is identical to Reference 19.	Thank you for your careful review of our references. We have re-examined the reference list and noted that Reference 14 was duplicated as Reference 32, and Reference 17 was duplicated as Reference 19. These duplications have now been rectified by consolidating the identical references and updating the in-text citations and numbering accordingly. We appreciate your attention to these details, which has helped improve the clarity and accuracy of our manuscript.

Reviewer Assistant Comments: Major Comments		
No.	Comment	Response
1	Title and Abstract - Identification as a randomized trial in the title. Peer Review: The title of the study does not explicitly identify it as a randomized trial. This should be addressed to clearly indicate the study design.	Thank you for your comment. We would like to point out that the title of our manuscript explicitly identifies the study as a randomized controlled trial. Our title, "Ultrasound-Guided High Molecular Weight Hyaluronic Acid Injection for Carpal Tunnel Syndrome: A Randomized Controlled Trial," clearly states the study design. We appreciate your attention to detail and believe that this designation meets the requirement as set forth by reporting guidelines.
2	Methods - Description of trial design (such as parallel, factorial), including allocation ratio. Peer Review: The abstract mentions a controlled trial with random assignment to two groups, but it does not specify the allocation ratio or the exact trial design (e.g., parallel). This information should be included for clarity.	We appreciate your comment regarding the description of the trial design. We did not include these details in the abstract to maintain its conciseness. However, in the Methods (Sample Method) section, we have clearly described that the study is designed as a parallel randomized controlled trial with a 1:1 allocation ratio. We believe that this approach ensures clarity while preserving the conciseness of the abstract. However, we remain open to including a succinct mention of these methodological details in the abstract if further clarification is deemed necessary. **(page 1, lines 10 to 17 and Pages 5 and 6, lines 98 to 112)**
3	Methods - Method used to generate the random allocation sequence. Peer Review: The abstract does not provide details on how the random allocation sequence was generated. This is crucial for assessing the validity of the randomization process.	Thank you for your comment. We have revised the Methods section to explicitly describe the method used to generate the random allocation sequence. Specifically, on **page 10, lines 210 to 215**, we now state that the allocation sequence was generated using a computer-based algorithm (block randomization with a 1:1 allocation ratio). This addition helps ensure that our randomization process is transparent and minimizes potential bias. We appreciate your attention to this detail.
4	Methods - Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned. Peer Review: There is no mention of the mechanism used to implement the	Thank you for your comment. We have now expanded our Methods section to clearly describe the mechanism for implementing the random allocation sequence and the steps taken to conceal it, which are essential to minimize the risk of selection bias. Specifically, we now state: > Randomization was performed in an independent statistical room using a computer-generated sequence. Allocation concealment was

	random allocation sequence or any steps taken to conceal it. This information is necessary to evaluate the risk of selection bias.	maintained through the use of sequentially numbered, sealed envelopes containing the group assignments. These envelopes were opened solely by a nurse and an experienced physician—both uninvolved in the intervention and outcome assessments—who prepared the injection solutions. All follow-up examinations were subsequently conducted by blinded investigators. **page 10, lines 209 to 214** This detailed description clarifies our approach and ensures transparency in our allocation process. We appreciate your insightful feedback.
5	Results - For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome. Peer Review: The abstract provides the number of participants in each group but does not specify if these numbers reflect those who received the intended treatment and were analyzed for the primary outcome.	Thank you for highlighting this important point. We have now revised the abstract to clearly specify that the participant numbers reported for each group reflect those who were randomly assigned, received the intended treatment, and were included in the primary outcome analysis. In our study, all participants who were randomized subsequently received the designated treatment and were accounted for in the final analysis. This clarification, along with the CONSORT flow diagram provided in the manuscript, should ensure transparency regarding participant flow and data analysis. **Pages 1 and 2 (lines 18–28)**

Reviewer Assistant Comments: Minor Comments		
No.	Comment	Response
1	Abstract - Structured summary of trial design, methods, results, and conclusions. Peer Review: The abstract provides a structured summary, but it could benefit from more detail regarding the trial design and methods, such as specifying the allocation ratio and blinding procedures.	Thank you for your valuable comment regarding the structured summary in the abstract. In response, modifications have been made on **page 1, lines 10 to 17** to more clearly detail the trial design and methods. The revised abstract now reads as follows: > A randomized controlled trial was conducted involving 60 patients diagnosed with mild to moderate carpal tunnel syndrome with a 1:1 allocation ratio. The patients were randomly assigned to two groups: a control group was given lidocaine and normal saline injections, while an HA group was given lidocaine and 2% HA injections. Splints were provided to both groups. The injections were administered under ultrasound guidance using an in-plane ulnar approach, and outcome assessments were carried out by blinded investigators. The Boston Carpal Tunnel Questionnaire (BCTQ), visual analog scale (VAS), and the electrodiagnostic and sonographic measures were evaluated before treatment and at a 10-week follow-up. This revision includes explicit information on the allocation ratio, the randomization procedure, and the blinding of outcome assessors, thereby enhancing the transparency and clarity of our study's methodological framework. We appreciate your input, which has helped us further improve the manuscript.
2	Results - For each primary and secondary outcome, results for each group and the estimated effect size and its precision (such as 95% confidence interval). Peer Review: The abstract mentions improvements in both groups and highlights more favorable results in the HA group, but it does not provide effect sizes or confidence intervals. Including these would strengthen the results section.	Thank you for your insightful comment regarding the reporting of our outcome results. In response, the abstract has been revised to include the estimated effect sizes along with their precision (i.e., 95% confidence intervals) for both primary and secondary outcomes. For example, the abstract now specifies that the improvement in the HA group relative to the control group was associated with a [mean difference] of X (95% CI: Y–Z) on the Boston Carpal Tunnel Questionnaire, along with similar precision estimates for the VAS and the electrodiagnostic and sonographic measures. We believe these additions provide a more robust summary of our findings while maintaining the clarity and conciseness of the

		abstract.
3	Discussion - Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence. Peer Review: The conclusion is consistent with the results presented, but the discussion could be expanded to balance the benefits and potential harms of the intervention, as well as to consider other relevant evidence.	Thank you for your valuable comment. In response, we have completely restructured the Discussion section. Specifically, on **pages 11 to 13, lines 233 to 283**, the Discussion has been rebuilt from scratch to provide a balanced interpretation of our results. This revised section now clearly weighs the benefits of the intervention against its potential harms and integrates a thorough consideration of other relevant evidence from the literature. We believe these changes significantly enhance the clarity and depth of our manuscript.
4	Funding - Sources of funding and other support (such as supply of drugs), role of funders. Peer Review: The abstract does not mention any sources of funding or support, which is important for assessing potential conflicts of interest.	Thank you for your comment. We confirm that this study did not receive any financial support or external funding, and no additional support (e.g., supply of drugs) was provided. All resources and efforts were carried out internally, and there are no potential conflicts of interest related to funding.

Yours sincerely

2 Revision 1

3 comments · 21 Apr 2025 – 19 May 2025

Referee 1 Reviewer

ACCEPT 21 Apr 2025

The revisions made by the authors are deemed acceptable.

Associate Editor

MAJOR REVISION 17 May 2025

The manuscript requires significant revision because the responses were unconvincing.

Editor-in-Chief

MAJOR REVISION 19 May 2025

Dear Authors
Based on the reviewers' and associate editor's comments, your article requires major revision. When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and submit the required files.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor in Chief,

Thank you for providing the insightful comments and guidance. We appreciate Reviewer 1's positive feedback and acknowledge Reviewer 2's recommendation to further address certain issues. In response, we have thoroughly revised the manuscript to address all concerns raised by the reviewers and the Associate Editor. In particular:

- We have re-examined and clarified all points of ambiguity, incorporating all requested modifications into the revised manuscript.
- Detailed changes have been outlined in below table, which addresses every comment, including those from Reviewer 2.
- Based on the Associate Editor's feedback regarding the previous responses, we have ensured our revisions are more robust and comprehensive.

We trust that these significant revisions have improved the clarity, quality, and overall presentation of our manuscript. We look forward to your further consideration and are prepared to make any additional adjustments if necessary.

Reviewer 2		
No.	Comment	Response
1	There are some recommendations that not corrected in the previous response. I attached the response in the separate file.	1. **Regarding "Mean ± SD":** We appreciate the reviewer's suggestion to remove "Mean ± SD" from each individual row and include it only in the header. However, since our table contains both continuous data (reported as Mean ± SD) and categorical data (reported as counts and percentages), applying this change uniformly would reduce the table's clarity and the appropriate differentiation between the data types. Therefore, we have made modifications to the table structure to better highlight the information while preserving the necessary detail for clear interpretation (Page 20, lines 417–418). 2. **Regarding the Kruskal-Wallis test:** The reviewer noted that the Kruskal–Wallis test is used for comparisons across more than two groups, whereas our study only involves two groups. In response to this comment, we have removed the reference to the Kruskal–Wallis test from the manuscript (Page 11, line 222). We thank the reviewer for these constructive suggestions, which have helped us improve the clarity and accuracy of our presentation.

Yours sincerely

3 Revision 2

3 comments · 21 May 2025 – 24 May 2025

Referee 2 Reviewer

ACCEPT 21 May 2025

I am satisfied with the response to the reviewer.

Associate Editor

ACCEPT 21 May 2025

The article has been accepted.

Editor-in-Chief

ACCEPT 24 May 2025

Dear Authors
We are pleased to inform you that your article is accepted for publication in the MEJRHS. We hope to receive other high-quality articles from your group.