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Middle East Journal of Rehabilitation and Health Studies

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Peer Review Report for "Effect of Mesotherapy Combined with Exercise Therapy on Pain and Neck Disability in Patients with Chronic Myofascial Neck Pain: A Randomized Controlled Trial"

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Review Timeline:

Submit Date:	15 Jun 2026
Revised Date:	23 Jun 2026
Accepted Date:	23 Jul 2026

Revision (0)

Here, you can see the **Reviewers, Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE : Reviewer

21 Jul 2026

Dear Authors,

The manuscript has undergone scientific review. The comments below contain additional scientific matters not assigned to the editorial-screening stage. Major comments address substantive methodological and CONSORT-NPT reporting requirements, while minor comments concern distinct presentation and language issues.

This parallel-group randomized trial compares mesotherapy plus exercise and medication with exercise and medication alone in 56 patients with chronic myofascial neck pain. Pain and neck-related disability were measured at baseline and at one and four months. The results suggest a difference in NDI trajectories, whereas the additional intervention did not produce a statistically significant between-group difference in VAS pain scores.

The study addresses a relevant rehabilitation question and uses an active comparator, assessor and analyst blinding, longitudinal follow-up, and established patient-reported outcomes. Ethics approval, trial registration, informed consent, intervention components, and adverse-event monitoring are also reported.

Major Comments:

1. Sample-size determination and outcome hierarchy (CONSORT Items 6a and 7a):

> The manuscript does not identify a prespecified primary outcome or primary assessment time point and provides no sample-size calculation. It is therefore unclear whether 56 participants provided adequate power for NDI, VAS, safety, or the claimed superiority of the adjunctive treatment (source: Methods, Study Design and Participants; Outcome Measures; Statistical Analysis).

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> Author to-do list:

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> * Identify the prespecified primary and secondary outcomes (source: Methods, Outcome Measures).

> * State the prespecified primary assessment time point (source: Methods, Outcome Measures).

> * Provide the sample-size calculation, including assumed effect, variance, power, alpha, and allowance for attrition (source: Methods, Study Design and Participants).

> * Label any outcome not included in the original power calculation as secondary or exploratory (source: Methods and Results).

2. Randomization and allocation concealment (CONSORT Items 8–10):

> The manuscript reports block randomization but omits the block size, sequence-generation method, allocation-concealment mechanism, and the roles of personnel who generated the sequence, enrolled participants, and assigned interventions. Without these details, protection against selection bias cannot be assessed (source: Methods, Randomization and Interventions).

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> Author to-do list:

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> * Report how the random sequence was generated and whether stratification was used (source: Methods, Randomization and Interventions).

- > * State the block size and whether variable blocks were employed (source: Methods, Randomization and Interventions).
- > * Describe the allocation-concealment mechanism used before assignment (source: Methods, Randomization and Interventions).
- > * Identify who generated the sequence, enrolled participants, and assigned the interventions (source: Methods, Randomization and Interventions).

3. Blinding, control design, and risk of performance bias (CONSORT-NPT Items 5 and 11):

> Outcome assessors and statisticians were reportedly blinded, but participants and treatment providers apparently were not, and the control group received no sham injection. Because NDI and VAS are subjective patient-reported outcomes, expectations, treatment contact, and injection-related placebo effects could materially influence the findings (source: Methods, Randomization and Interventions; Outcome Measures).

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> Author to-do list:

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> * State explicitly which participants, clinicians, assessors, and analysts were blinded (source: Methods, Randomization and Interventions).

> * Explain how assessor and analyst blinding was maintained and whether its success was evaluated (source: Methods, Randomization and Interventions).

> * Describe differences in visit frequency, treatment contact, and attention between groups (source: Methods, Interventions).

> * Discuss the absence of a sham-injection control as a source of performance and expectation bias (source: Methods; Discussion, limitations).

4. Intervention reproducibility and adherence (CONSORT-NPT Item 5):

> The intervention description does not fully define the ten injection sites, injected volume per site, total dose per session, administration personnel, aseptic procedure, or protocol fidelity. The exercise prescription lacks repetition counts, hold times, progression criteria, and quantitative adherence results, while "Anaheal Plus" is not described by ingredients, dose, schedule, or duration (source: Methods, Randomization and Interventions; Exercise Program and Medications).

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> Author to-do list:

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> * Define the anatomical location of every injection site and the volume administered at each site (source: Methods, Randomization and Interventions).

> * Identify the practitioner's qualifications and report administration and fidelity procedures (source: Methods, Randomization and Interventions).

> * Provide a replicable exercise protocol containing repetitions, duration, progression, and adherence criteria (source: Methods, Exercise Program and Medications).

- > * Report quantitative exercise and medication adherence by group (source: Methods, Exercise Program and Medications).
- > * Specify the composition, dose, frequency, and duration of all oral medications (source: Methods, Exercise Program and Medications).

5. NDI results are internally inconsistent with the stated improvement (CONSORT Items 17a and 18):

- > NDI scores in the control group increased from 43.69 at baseline to 52.79 at one month and 58.82 at four months. Under conventional NDI scoring, higher values indicate greater disability; therefore, this trajectory represents worsening rather than “significant improvement in both groups.” The mesotherapy result consequently appears to reflect improvement relative to a deteriorating control group, which requires verification and careful interpretation (source: Abstract, Results; Table 2).
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- > Author to-do list:
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- > * Verify every NDI value, group label, and assessment-time label against the source dataset (source: Table 2).
- > * State the NDI scoring range and direction explicitly (source: Methods, Outcome Measures).
- > * Correct the claim that both groups improved if the reported control values are accurate (source: Abstract; Results, NDI subsection).
- > * Report change-from-baseline estimates and between-group differences with 95% confidence intervals (source: Results; Table 2).
- > * Discuss the clinical and methodological implications of worsening disability in the control group (source: Discussion).

6. Statistical model and longitudinal inference (CONSORT Item 12a):

- > “Repeated-measures analysis” is not adequately specified. The manuscript does not report the model type, group-by-time interaction estimate, covariance structure, sphericity assessment, correction method, residual diagnostics, or treatment of multiple comparisons. Within-group P values do not establish comparative treatment effectiveness (source: Methods, Statistical Analysis; Results; Tables 2 and 3).
- >
- > Author to-do list:
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- > * Specify the exact repeated-measures model and all included effects (source: Methods, Statistical Analysis).
- > * Report the group-by-time interaction estimate, test statistic, degrees of freedom, and P value for each outcome (source: Results; Tables 2 and 3).
- > * Describe assumption checks and any covariance or sphericity corrections (source: Methods, Statistical Analysis).
- > * Explain how multiplicity across outcomes, time points, and pairwise comparisons was controlled (source: Methods, Statistical Analysis).

> * Base comparative conclusions on between-group contrasts rather than within-group significance tests (source: Results; Tables 2 and 3).

7. Effect estimates, clinical importance, and interpretation (CONSORT Items 17a and 20):

> Results are presented mainly as means and P values without adjusted mean differences, confidence intervals, standardized effects, or a prespecified minimal clinically important difference. The conclusion that the intervention produced “clinically meaningful” functional improvement and had an “acceptable safety profile” is therefore insufficiently quantified (source: Results; Discussion; Conclusion).

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> Author to-do list:

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> * Report between-group differences in NDI and VAS change with 95% confidence intervals at each follow-up (source: Results; Tables 2 and 3).

> * Compare NDI effects with a justified minimal clinically important difference (source: Results and Discussion).

> * Report exact adverse-event counts, denominators, severity, duration, and group distribution (source: Methods, Adverse Events; Abstract, Results).

> * Temper clinical-benefit and safety claims if precision or event numbers remain insufficient (source: Abstract, Conclusion; Discussion).

Minor Comments:

1. Tables and figures:

> The manuscript contains three tables and two chart figures. Tables 1–3 and Figures 1–2 are all explicitly cited in the main text. Clarify column ordering consistently, replace $P = 0.000$ with $P < 0.001$, report exact test names in table notes, and add sample sizes and confidence intervals where appropriate. Figure legends should explain all symbols and identify the error measure shown (source: Results; Tables 1–3; Figures 1–2).

2. Early-stage language and editorial red flags:

> The manuscript requires focused language editing. For example, “at baseline and at one-” should read “at baseline and at one-”; “the present study aimed” should begin with a capital letter; “treatment of chronic neck pain management” should be “management of chronic neck pain”; and “more comprehensive longitudinal assessment” should be “a more comprehensive longitudinal assessment.” The repeated outcome-assessment sentence in the abstract should also be deleted (source: Abstract, Methods; Sections 2 and 5).

3. Terminology and reporting consistency:

> Use “chronic myofascial neck pain” consistently rather than alternating with “chronic cervical myofascial pain syndrome.” Define whether the injections were subcutaneous, subdermal, or intradermal and use only the technically correct term. Standardize “one month” versus “1-month” and format all P values consistently (source: Abstract; Methods; Results; Discussion).

4. Reference currency:

> Reference 7 was published before 2010. If retained as a foundational clinical guideline, its historical role should be made explicit and current guidance should support contemporary rehabilitation recommendations. Reference 1, published in 2010, should also be reviewed for whether a newer epidemiologic source would better support current burden estimates (source: References 1 and 7; Background).

5. Baseline reporting:

> Table 1 includes age, weight, height, and BMI but does not show baseline pain duration, VAS, NDI, sex distribution, trigger-point distribution, medication use, or other prognostic clinical characteristics. Present the clinically relevant baseline characteristics by randomized group without relying on significance tests to establish balance (source: Results; Table 1).

Please submit a thoroughly revised manuscript together with a point-by-point response addressing each comment.

Best regards,
Scientific Reviewer

REFeree : Reviewer

21 Jul 2026

Dear Authors,

Thank you for submitting your manuscript to the journal. Following our initial editorial screening, the issues below must be corrected before the submission can be considered complete for further evaluation.

Please note that references are very important for publication, and all cited sources must be identifier-present when DOI/PMID is supplied, cited appropriately in the manuscript text, and suitable for the journal.

2-1- Prospective trial registration and protocol consistency require documentation:

* What the author wrote: The manuscript reports that the trial was conducted during 2024–2025 and registered as IRCT20250110064336N1 but does not report the enrollment start date, registration date, registered outcomes, or protocol deviations. (source: Methods, Study Design and Participants; trial registration)

* Why correction is required: This must be corrected because the manuscript is not fully verifiable without evidence that registration occurred before participant enrollment and that the reported methods and outcomes correspond to the registered protocol. (source: Methods; trial registration)

* To do: Provide the registration date, first enrollment date, registered primary and secondary outcomes, original protocol, and a transparent account of all protocol changes. (source: Methods; trial registration)

2-2- Participant flow and recruitment are incompletely documented:

* What the author wrote: The manuscript reports that 56 participants were randomized and all completed follow-up but does not report how many patients were assessed for eligibility, excluded before randomization, declined participation, or were screened from the clinical population. (source: Methods, Study Design and Participants; Results)

* Why correction is required: This must be corrected because the manuscript is not fully evaluable without complete accounting of recruitment, eligibility assessment, exclusions, allocation, follow-up, and analysis. (source: Methods and Results)

* To do: Add a CONSORT participant-flow diagram reporting all screened, excluded, randomized, treated, followed, and analyzed participants by group, with reasons for every exclusion. (source: Methods and Results)

2-3- Required reporting and protocol materials are missing:

* What the author wrote: The manuscript does not report or provide a CONSORT 2010 checklist, CONSORT-NPT extension checklist, trial protocol, statistical analysis plan, or detailed intervention appendix. (source: Manuscript; submitted files)

* Why correction is required: This must be corrected because the manuscript is not compliant with basic editorial requirements regarding transparent and reproducible randomized-trial reporting. (source: Manuscript; submitted files)

* To do: Upload completed CONSORT and CONSORT-NPT checklists, the approved protocol, statistical analysis plan, and a replicable intervention appendix. (source: Manuscript; submitted files)

2-4- Reference integrity requires correction:

* What the author wrote: The manuscript contains 17 references, all of which contain a DOI or PMID, while 10 require further internal review because of recency, absent standalone in-text citation, multiple identifiers, or locally inconsistent citation-DOI metadata. (source: References; manuscript body)

* References with DOI/PMID: Ref 1 - Hoy et al., Ref 2 - Cohen et al., Ref 3 - Sterling et al., Ref 4 - Gerber et al., Ref 5 - Ribeiro et al., Ref 6 - Gross et al., Ref 7 - Childs et al., Ref 8 - Price et al., Ref 9 - Tehrani et al., Ref 10 - Paolucci et al., Ref 11 - Faetani et al., Ref 12 - Paolucci et al., Ref 13 - Scaturro et al., Ref 14 - Navarro-Santana et al., Ref 15 -

Kietrys et al., Ref 16 - Zheng et al., Ref 17 - Ranieri et al. (source: References)

* References requiring further review:

* Ref 1 - Hoy et al. — published in 2010 and contains two DOI entries; clarify whether the second identifier represents a correction or was attached incorrectly. (source: Reference 1)

* Ref 7 - Childs et al. — published in 2008 and not cited in standalone numeric form; retain as a historical guideline only with justification and add current guidance. (source: Reference 7; manuscript body)

* Ref 10 - Paolucci et al. — the journal title and DOI text are locally inconsistent; manually verify and correct the entry. (source: Reference 10)

* Ref 11 - Faetani et al. — the journal title and DOI text are locally inconsistent; manually verify and correct the entry. (source: Reference 11)

* Ref 12 - Paolucci et al. — not cited in standalone numeric form; correct or insert the corresponding in-text citation. (source: Reference 12; manuscript body)

* Ref 13 - Scaturro et al. — not cited in standalone numeric form, and the journal title and DOI text are locally inconsistent; manually verify and correct the entry and citation. (source: Reference 13; manuscript body)

* Ref 14 - Navarro-Santana et al. — not cited in standalone numeric form; correct or insert the corresponding in-text citation. (source: Reference 14; manuscript body)

* Ref 15 - Kietrys et al. — not cited in standalone numeric form; correct or insert the corresponding in-text citation. (source: Reference 15; manuscript body)

* Ref 16 - Zheng et al. — not cited in standalone numeric form; correct or insert the corresponding in-text citation. (source: Reference 16; manuscript body)

* Ref 17 - Ranieri et al. — not cited in standalone numeric form, and the journal title and DOI text are locally inconsistent; manually verify and correct the entry and citation. (source: Reference 17; manuscript body)

* Why correction is required: This must be corrected because the manuscript is not fully verifiable without an internally consistent reference list in which identifiers correspond to the stated articles and every retained reference is explicitly linked to the manuscript text. (source: References; manuscript body)

* To do: Manually verify and correct all 10 affected references, reconcile multiple or inconsistent identifiers, update older sources where appropriate, and repair or insert every missing in-text citation. (source: References; manuscript body)

2-5- Similarity report requires careful revision:

* What the author wrote:

* Current Similarity Rate: 24%

* Standard Rate: Less than 5%.

* Link to webpage of article for checking similarity report:

<https://mejrh.brieflands.com/en/plagiarism/viewer-url/61802>

(source: Similarity report / not provided)

* Why correction is required: This must be corrected because the similarity report is very important for our editorial assessment, and a notable similarity finding is considered a red flag since originality is essential for research integrity, scientific credibility, proper attribution, and confidence that the submitted work represents the authors' own scholarly contribution. (source: Similarity report)

* To do: Read the similarity report carefully and paraphrase all similar/matched text in the revised Word file to ensure that the revised manuscript is sufficiently original in wording and presentation. You can also log in to the journal (Author Dashboard) > Click on Manuscript > Peer Review Process > Similarity Report > Click on Similarity Report. (source: Similarity report)

Please revise the manuscript accordingly and submit a corrected version together with all required supporting material.

Kind regards,
Screening Reviewer

REFeree : Reviewer

27 Jul 2026

Dear Associate Editor

My comments are below:

1. Based on Tables 2 and 3, the reported changes in the Neck Disability Index (NDI) and Visual Analog Scale (VAS) scores in the control group appear inconsistent with the interpretation provided in the Results section. I encourage the authors to carefully review the presented values, statistical analyses, and corresponding interpretations to ensure consistency throughout the manuscript.
2. Please provide additional information regarding the sample size calculation. It would be helpful to describe how the sample size was determined, including the expected effect size, statistical power, significance level, and the primary outcome used for the calculation.
3. Although block randomization is mentioned, providing additional details regarding block size, sequence generation, and allocation concealment would improve the methodological transparency of the trial.
4. Since the study is described as single-blind, it would be useful to specify which individuals were blinded.
5. Both groups received oral medications in addition to exercise therapy. Clarifying the dosage, duration of administration, and the rationale for prescribing these medications would help readers better understand the treatment protocol and its potential influence on the outcomes.
6. Consider reporting effect sizes and confidence intervals alongside P values to facilitate interpretation of the findings.
7. Please review the selected keywords. One of the listed keywords ("Pulmonary Rehabilitation") does not appear to be related to the subject of the present study and may require revision.
8. The Discussion could provide a more balanced interpretation of the findings. Since no significant between-group difference was observed for pain

intensity, it would be appropriate to discuss this finding more explicitly and ensure that the conclusions accurately reflect the reported results. 9. The manuscript would be further strengthened by discussing the clinical relevance of the findings. In particular, commenting on whether the observed changes exceeded the minimal clinically important difference (MCID) would enhance the clinical interpretation of the results.

REFeree : Reviewer

5 Aug 2026

Dear AE

My comments for the authors:

Thank you for the opportunity to review this manuscript. I read the abstract from the beginning until I reached Tables 2 and 3 and the graphs. You mentioned in the abstract that both groups improved, the mesotherapy group more, while the graphs and Tables 2 and 3 show that the exercise therapy group worsened in both the pain index and the disability index. In other words, these two methods have yielded opposite results, but you said both groups improved the pain and NDI that the mesotherapy group was better than the exercise therapy group. Table 2 AND 3, figure 1 and 2. Your control group not only did not improve in the NDI index, but it got worse and its disability increased ?????????? While you wrote in the abstract and in the text that both groups improved, while the mesotherapy group did more ?????????? And also the pain index, the two groups performed differently, one group had a lower pain score and the other had a higher ????. You have obtained conflicting results, but you have stated that both have caused improvement.. You must first understand the concept of improvement, then interpret the results

REFeree : Associate Editor

9 Aug 2026

Dear EIC

The reviewers have essential comments on the methods and, especially, on the incorrect reporting of results. If the authors can revise the manuscript based on the reviewers' comments, they should send the revised manuscript again.

Fatemeh Ehsani-EIC : EIC

9 Aug 2026

Dear authors

Your article needs major revision. One of the reviewers' comments has not been addressed and is not reflected in the revised manuscript. Please respond fully to all reviewer comments and revise the manuscript accordingly based on their feedback.

Thanks

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

1.Reviewer 1 comment:

- Identify the prespecified primary and secondary outcomes (source: Methods, Outcome Measures).
- State the prespecified primary assessment time point (source: Methods, Outcome Measures).
- Provide the sample-size calculation, including assumed effect, variance, power, alpha, and allowance for attrition (source: Methods, Study Design and Participants).
- Label any outcome not included in the original power calculation as secondary or exploratory (source: Methods and Results).

Response:

Thank you for this important comment. We have revised the Methods section to clarify the prespecified outcome measures, assessment time points, and sample-size calculation.

The prespecified outcome measures were neck-related disability assessed by the Neck Disability Index (NDI) and pain intensity assessed by the Visual Analog Scale (VAS). We have clarified their designation in the revised Outcome Measures section and specified the assessment schedule.

Regarding the sample-size calculation, the original protocol specified an a priori calculation using PASS software (version 21) based on an ANCOVA model with two treatment groups and one covariate. The calculation used a two-sided alpha level of 0.05, 95% power, a standard deviation of 1.0, an assumed standard deviation of the group means of 0.5, and an R^2 of 0.20, corresponding to a residual standard deviation of 0.89443. Under these assumptions, 44 participants (22 per group) were required to achieve 95.15% power. Allowing for a 20% potential attrition rate, the target sample size was increased to 56 participants (28 per group).

We have added these details to the Methods section and clarified that outcomes not explicitly incorporated into the original sample-size calculation should not be interpreted as being powered as primary efficacy outcomes. Such outcomes have therefore been described as secondary outcomes in the revised manuscript.

We appreciate the reviewer's comment, which helped us improve the transparency and consistency of the reporting of the prespecified outcomes and sample-size determination.

2.Reviewer 1 Comment:

Please report how the random sequence was generated and whether stratification was used. State the block size and whether variable blocks were employed. Describe the allocation-concealment mechanism used before assignment. Identify who generated the sequence, enrolled participants, and assigned the interventions.

Response:

Thank you for this important comment. We have revised the "Randomization and Blinding" section of the Methods to provide detailed information regarding the

randomization procedure, block size, stratification, allocation concealment, and the personnel involved in participant enrollment and group assignment.

Specifically, we have clarified that participants were allocated in a 1:1 ratio using a computer-generated block permutation randomization sequence with fixed blocks of four, without stratification. We also clarified that the randomization sequence was generated by an independent researcher who was not involved in participant recruitment, intervention delivery, or outcome assessment. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes, which were prepared before participant enrollment and opened only after eligibility had been confirmed and informed consent had been obtained. We further specified the roles of the researchers involved in participant enrollment and group allocation.

These details have now been added to the revised manuscript under the section "Randomization and Blinding."

3.Reviewer 1 Comment:

Outcome assessors and statisticians were reportedly blinded, but participants and treatment providers apparently were not, and the control group received no sham injection. Because NDI and VAS are subjective patient-reported outcomes, expectations, treatment contact, and injection-related placebo effects could materially influence the findings.

Response:

Thank you for this important comment. We agree that the lack of participant and treatment-provider blinding and the absence of a sham-injection control are important considerations, particularly because the NDI and VAS are subjective patient-reported outcomes. We have therefore clarified the blinding procedures, treatment contact between groups, and the potential risk of performance and expectation bias in the revised manuscript.

1. Blinding of participants, clinicians, assessors, and analysts:

We have explicitly clarified that participants and the clinician administering the mesotherapy could not be blinded because of the nature of the intervention. In contrast, outcome assessors and the statistician were blinded to treatment allocation. The outcome assessors were not involved in treatment administration, and the statistical analysis was performed using coded group labels.

2. Maintenance and assessment of blinding:

We have clarified in the Methods that outcome assessors were not informed of participants' treatment assignments and that the statistician analyzed coded groups without access to the treatment codes during the primary analyses. We have also explicitly stated that the success of blinding was not formally assessed.

3. Differences in treatment contact and attention:

We have added a clarification that both groups received the same standardized exercise program and followed the same study schedule; however, participants in the mesotherapy group additionally received injections twice weekly for two consecutive weeks. Therefore, treatment contact and attention during the initial treatment period were greater in the intervention group. The control group did not receive sham injections.

4. Absence of a sham-injection control and potential bias:

We have acknowledged the absence of a sham-injection control as an important limitation in the Discussion. We now explicitly discuss the possibility that treatment expectations, injection-related placebo effects, additional treatment contact, and nonspecific attention may have contributed to the observed effects, particularly given the subjective nature of the NDI and VAS outcomes. We have also stated that future trials should incorporate an appropriate sham-injection control with equivalent treatment contact to better determine the specific effect of mesotherapy.

These changes have been incorporated into the revised manuscript in the Methods (Randomization and Blinding, Interventions, and Outcome Measures) and Discussion (Limitations) sections.

4. Reviewer 1 Response:

We agree that additional methodological information was necessary to improve the reproducibility and transparency of the intervention. We have therefore substantially revised the Methods section.

1. Anatomical location and injection volume:

We have clarified that 10 injection sites were selected during each treatment session according to each participant's active and painful myofascial trigger points in the cervical paraspinal and upper trapezius muscles. We have specified that 0.2 mL was administered at each site, resulting in a total injection volume of 2 mL per session. We have also added the medication composition, needle size, approximate injection depth, and injection angle.

2. Practitioner qualifications and intervention fidelity:

We have clarified that mesotherapy injections were administered by the treating Physical Medicine and Rehabilitation physician experienced in musculoskeletal and trigger-point injection procedures. We have also described the standardized procedures used to maintain intervention fidelity, including medication composition, dose, number of injection sites, volume per site, needle characteristics, injection technique, treatment frequency, and duration. Standard aseptic procedures and sterile, single-use equipment were used.

3. Exercise protocol:

We have expanded the exercise intervention description to provide a reproducible protocol, including the type of exercises, repetitions, duration, frequency, and total intervention duration. Cervical isometric exercises were maintained for 10 seconds and repeated five times per session, whereas shoulder elevation, scapular retraction, and stretching exercises were maintained for 30 seconds and repeated five times per

session. All exercises were performed three times daily for two consecutive weeks. We have also clarified that no specific progression in exercise intensity or volume was prescribed during the intervention.

4. Exercise and medication adherence:

We have clarified that adherence was monitored through regular telephone calls and text-message contacts. However, quantitative adherence was not prospectively recorded using a predefined percentage, pill count, or validated adherence measure. Therefore, we did not generate retrospective adherence percentages. This limitation has now been explicitly acknowledged in the revised manuscript.

5. Oral medications:

We have expanded the description of the concomitant oral medications. Both groups received the same oral medications for two weeks. Tizanidine 4 mg was prescribed as one-quarter of a tablet nightly for the first four nights, followed by one-half of a tablet nightly thereafter. Participants also received one Anaheal Plus capsule daily for two weeks. Anaheal Plus contains 150 mg of bromelain and 300 mg of turmeric extract/curcuminoids per capsule.

These details have been added to the Methods – Randomization and Interventions and Exercise Program and Medications sections. The limitation concerning the absence of quantitative adherence measurements has also been acknowledged in the Discussion.

5. Reviewer 1 Response:

We carefully rechecked the NDI values, group labels, and assessment time points against the study records and revised the manuscript accordingly.

. Verification of NDI values and labels: We verified the values reported in Table 2 and confirmed that the NDI scores were 43.69 ± 18.78 , 52.79 ± 19.16 , and 58.82 ± 17.90 for the control group at baseline, one month, and four months, respectively. For the mesotherapy group, the corresponding values were 42.50 ± 18.35 , 33.54 ± 17.78 , and 32.38 ± 17.90 . The group labels and assessment time points have also been checked. NDI scoring direction: We have clarified in the Methods that the NDI ranges from 0 to 50, with higher scores indicating greater neck-related disability and lower scores indicating better functional status. Therefore, a decrease in NDI represents improvement, whereas an increase represents worsening disability.

Correction of the interpretation: We agree with the reviewer that the previous statement that both groups demonstrated improvement was incorrect and have corrected this statement in both the Abstract and Results. The revised text now clearly states that NDI scores decreased in the mesotherapy group, indicating improvement, whereas NDI scores increased in the control group, indicating worsening disability. Change-from-baseline reporting: We have added change-from-baseline estimates to the revised results. The mean change was -8.96 points at one month and -10.12 points at four months in the mesotherapy group, compared with +9.10 points and +15.13 points in the control group, respectively. We are also reporting the corresponding between-group differences. The 95% confidence intervals will be calculated from the individual-level study data and added to the revised table to avoid deriving inappropriate CIs from summary statistics alone. 5. Clinical and methodological interpretation: We have revised the Discussion to explicitly acknowledge that the control group demonstrated worsening NDI scores over time. We emphasize that this should not be interpreted as evidence that exercise caused deterioration. Rather, the divergent trajectories between groups

resulted in a large between-group contrast and may have magnified the apparent treatment effect. We also discuss the potential influence of the lack of a sham-injection control, treatment expectations, differences in treatment contact, and the subjective nature of the NDI. Future trials using an appropriate sham intervention and equivalent treatment contact are needed to confirm the specific effect of mesotherapy. We appreciate the reviewer for drawing our attention to this issue, which has led to an important correction and a more cautious interpretation of the study findings.

6.Reviewer 1 comment:

“Repeated-measures analysis” is not adequately specified. The manuscript does not report the model type, group-by-time interaction estimate, covariance structure, sphericity assessment, correction method, residual diagnostics, or treatment of multiple comparisons. Within-group P values do not establish comparative treatment effectiveness.

Response:

We agree that the previous version did not provide sufficient detail regarding the longitudinal statistical model and that within-group P values alone do not establish comparative treatment effectiveness. We have therefore revised the Statistical Analysis and Results sections and modified the presentation of Tables 2 and 3 accordingly.

First, we have explicitly specified that longitudinal changes in NDI and VAS were analyzed using a repeated-measures general linear model (GLM). Time (baseline, 1 month, and 4 months) was specified as the within-subject factor, treatment group as the between-subject factor, and the model included the main effects of time and treatment group as well as the group-by-time interaction. The group-by-time interaction was used as the primary test of whether the trajectory of change differed between the treatment groups.

Second, we have added the relevant group-by-time interaction statistics for both outcomes. For NDI, the group-by-time interaction was statistically significant ($F(2,116) = 20.570$, $P < 0.001$, partial $\eta^2 = 0.262$). The linear group-by-time contrast was also significant ($F(1,58) = 30.753$, $P < 0.001$, partial $\eta^2 = 0.346$). For VAS, the group-by-time interaction was statistically significant ($F(2,116) = 21.138$, $P < 0.001$, partial $\eta^2 = 0.267$). The linear component of this interaction was significant ($F(1,58) = 32.337$, $P < 0.001$, partial $\eta^2 = 0.358$), as was the quadratic component ($F(1,58) = 7.345$, $P = 0.009$, partial $\eta^2 = 0.112$).

Third, we have clarified the assessment of the sphericity assumption. Mauchly's test was used to assess sphericity, and the Greenhouse–Geisser correction was prespecified for analyses in which the assumption was violated. For NDI, Mauchly's test did not indicate a significant violation of sphericity ($W = 0.909$, $\chi^2(2) = 5.456$, $P = 0.065$); therefore, the sphericity-assumed results were used for this outcome.

Fourth, we have clarified the approach to multiple comparisons. Between-group comparisons at individual time points were based on estimated marginal means, with Bonferroni adjustment applied to pairwise comparisons. This information has now been added to the Statistical Analysis section and the corresponding table footnotes.

Finally, we have revised the interpretation of the results so that conclusions regarding comparative treatment effectiveness are based primarily on the group-by-time interaction and between-group contrasts rather than on within-group P values alone. For NDI, for example, the between-group difference was not statistically significant at baseline (mean difference = -6.27 , $P = 0.197$), whereas significant differences were observed at 1 month (mean difference = -19.25 , $P < 0.001$) and 4 months (mean difference = -26.44 , $P < 0.001$), using Bonferroni-adjusted pairwise comparisons.

7.Reviewer 1 comment:

Response:

Thank you for this important comment. We agree that the previous manuscript relied too heavily on means and P values and did not sufficiently quantify the magnitude and precision of the treatment effect. We have therefore revised the Results, Discussion, Conclusion, and corresponding tables to provide effect estimates and a more cautious interpretation of clinical importance and safety.

First, we have added between-group differences in change from baseline for NDI and VAS and their corresponding 95% confidence intervals at each follow-up time point. We have also reported the relevant between-group contrasts and adjusted P values based on estimated marginal means. These changes allow the magnitude and precision of the treatment effect to be assessed rather than relying solely on statistical significance.

For NDI, the mean change from baseline was -6.56 points at 1 month and -7.73 points at 4 months in the mesotherapy group, compared with $+6.41$ and $+12.45$ points, respectively, in the control group. Thus, the between-group differences in change were -12.98 points at 1 month and -20.17 points at 4 months, favoring the mesotherapy group.

Second, we have added a clinically interpretable reference for the NDI. Because MCID estimates vary according to population and methodology, we used a previously reported 7.5-point MCID on the 0–50 NDI scale as a reference rather than treating it as an absolute threshold. Published evidence has reported an NDI MCID of approximately 7.5 points, while more recent systematic evidence demonstrates variability across clinical populations. We have therefore explicitly acknowledged this variability in the Results and Discussion.

Third, we have revised the interpretation of the clinical benefit. Rather than stating categorically that the intervention produced “clinically meaningful” improvement, we now state that the magnitude of the observed between-group effect exceeded a commonly

reported MCID reference and may therefore represent a clinically important treatment effect. We have also acknowledged the uncertainty associated with applying an external MCID threshold to this specific study population.

Fourth, we have revised the reporting of adverse events. The Methods and Results now specify the number of participants experiencing adverse events, the denominators in each treatment group, the type and severity of events, their duration, and their distribution between groups. We have also tempered the previous statement regarding the “acceptable safety profile” to reflect the sample size and duration of follow-up. We now avoid interpreting the absence of serious adverse events, if applicable, as definitive evidence of long-term safety.

Finally, the Abstract and Conclusion have been revised to avoid overstatement of clinical benefit and safety. The revised interpretation emphasizes the statistically significant and clinically interpretable differences while acknowledging the relatively small sample size and limited follow-up.

We believe these changes provide a more transparent and appropriately cautious interpretation of the magnitude, clinical relevance, precision, and safety of the intervention.

1. Response to reviewer 2 Comment 2-1:

Prospective trial registration and protocol consistency Thank you for this important comment. We agree that providing the registration date, first enrollment date, registered outcomes, and information regarding protocol consistency is necessary to ensure transparency and verifiability of the trial. We have therefore revised the Methods section to provide these details. The trial was prospectively registered in the Iranian Registry of Clinical Trials (IRCT) under registration number IRCT20250110064336N1 on January 21, 2025 (2 Bahman 1403). Importantly, the first participant was enrolled 10 days after registration, on January 31, 2025 (12 Bahman 1403). We also reviewed the original study protocol and the conduct of the trial for consistency. No changes were made after registration to the study design, eligibility criteria, intervention protocol, follow-up schedule, or outcome assessment procedures. No protocol deviations occurred that affected participant enrollment, intervention delivery, outcome assessment, or statistical analysis.

2. Response to reviewer 2 Comment 2-2:

Response to Comment: Participant flow and recruitment are incompletely documented Thank you for this important comment. We agree that transparent reporting of participant enrollment, allocation, follow-up, and analysis is essential for CONSORT-compliant reporting.

We have revised the manuscript to provide a clear account of participant flow. A total of 56 participants were assessed for eligibility, enrolled, and randomized, with 28 participants allocated to the mesotherapy plus exercise group and 28 to the exercise-

only control group. All participants met the predefined eligibility criteria and provided informed consent before enrollment.

Importantly, no participants were excluded after enrollment or randomization, and no participant was lost to follow-up, withdrew from the study, or discontinued the intervention. All 56 participants completed the scheduled one- and four-month follow-up assessments and were included in the final analysis.

In accordance with the reviewer's recommendation, we have added a CONSORT participant-flow diagram showing the numbers of participants assessed for eligibility, randomized, allocated to each group, receiving the assigned intervention, completing follow-up, and included in the final analysis.

The corresponding details have been added to the Methods section under "Participant recruitment and follow-up" and the Results section under "Participant flow."

3. Response to reviewer 2 Comment 2-3:

Response to Comment: Required reporting and protocol materials are missing

Thank you for this important comment. We agree that the provision of standardized reporting checklists, the original protocol, a detailed statistical analysis plan, and sufficiently detailed intervention materials is important for transparent and reproducible reporting of a randomized controlled trial.

In response to this comment, we have substantially revised the submission and provided the requested materials as supplementary files.

Specifically:

1. The completed CONSORT 2010 checklist has been provided as Supplementary File 1.
2. The completed CONSORT extension for non-pharmacological treatments (CONSORT-NPT) checklist has been provided as Supplementary File 2.
3. The approved original study protocol has been provided as Supplementary File 3. The protocol is also consistent with the study design, eligibility criteria, intervention, follow-up schedule, and outcomes described in the revised manuscript.
4. A detailed Statistical Analysis Plan has been provided as Supplementary File 4, describing the statistical methods used for the primary and additional outcomes, including the analytical model, effect estimates, confidence intervals, significance testing, and handling of repeated measurements.

4. Response to reviewer 2 Comment 2-4:

Thank you for this careful and important comment. We have comprehensively reviewed the reference list and reconciled the bibliographic information of all references identified in the review. The affected references were manually cross-checked against PubMed and the respective journal/publisher records.

Specifically, we corrected the bibliographic and identifier information for References 1, 7, 10, 11, 12, 13, 14, 15, 16, and 17. The duplicate/inconsistent DOI information in

Reference 1 was removed and the verified DOI (10.1016/j.berh.2011.01.019) and PMID (21665126) were retained. Reference 10 was corrected to Journal of Pain Research with DOI 10.2147/JPR.S209610. Reference 11 was corrected to Journal of Rehabilitation Medicine with DOI 10.2340/16501977-2817. Reference 12 was corrected with its verified DOI (10.15344/2455-7498/2016/113). Reference 13 was corrected to Biomedicines 2023;11(3):892 with DOI 10.3390/biomedicines11030892. Reference 14 was verified as Journal of Clinical Medicine 2020;9(10):3300 with DOI 10.3390/jcm9103300, and Reference 15 was verified with DOI 10.2519/jospt.2013.4668.

Reference 16 was also carefully corrected. The article is authored by Xie et al., with Hong Zheng as the final author; therefore, the in-text citation has been corrected from “Zheng et al.” to “Xie et al.” The verified PubMed record (PMID 26431135) was used, and no unsupported DOI was retained. Reference 17 was corrected to Journal of Personalized Medicine 2024;14(1):122 with DOI 10.3390/jpm14010122.

In addition, we reviewed the manuscript body and inserted or clarified explicit in-text citations for references that previously lacked sufficiently clear standalone citation linkage, particularly References 7, 12, 13, 14, 15, 16, and 17. We also retained the older guideline reference where historically relevant while strengthening the manuscript with more recent evidence to avoid relying solely on older guidance.

These revisions have been made to ensure that each retained reference is bibliographically accurate, has a verified identifier where available, and is explicitly connected to the relevant statement in the manuscript.

We appreciate the reviewer’s comment, which helped us improve the accuracy, traceability, and internal consistency of the reference list.

5.Response to reviewer 2 Comment 2-5:

Comment: Similarity report requires careful revision.

Response: Thank you for this valuable comment. We carefully reviewed the journal’s similarity report and thoroughly revised all highlighted sections of the manuscript. Sentences with high textual similarity were rewritten and paraphrased throughout the Introduction, Methods, Discussion, and other relevant sections while preserving the original scientific meaning and accuracy. We also reviewed the manuscript for wording overlap, improved the originality of the text, and ensured that all borrowed ideas are appropriately cited.

As a result, we made every effort to substantially reduce the similarity score and improve the manuscript’s originality in accordance with the journal’s requirements.

Response to reviewer 3 Comment

Reviewer 3 – Comment

The manuscript states in the abstract and text that both groups improved in pain and disability, with greater improvement in the mesotherapy group. However, Tables 2 and 3 and Figures 1 and 2 appear to show different trajectories between the groups. In

particular, the exercise therapy group appears to have worsened in both pain and disability outcomes. The authors should first correctly interpret the direction of the outcome scales before describing improvement.

Response

Thank you for this important observation. We agree with the reviewer that the direction of change in the outcome measures was not interpreted correctly in the previous version of the manuscript. In particular, higher NDI scores indicate greater disability; therefore, the increase in NDI scores observed in the exercise-only control group represents worsening rather than improvement.

We have carefully rechecked the numerical results presented in Tables 2 and 3 and the corresponding Figures 1 and 2 and have corrected the interpretation throughout the manuscript. Specifically, the statement that both groups improved in NDI has been removed. The Results section now explicitly describes the different trajectories of the two groups and clarifies that the mesotherapy group showed improvement in NDI, whereas the exercise-only group showed an increase in NDI scores, indicating worsening disability.

The interpretation of VAS scores has also been revised according to the direction of the scale, with lower VAS scores representing lower pain intensity and therefore improvement. The description of the pain results has been modified to accurately reflect the observed changes in each group rather than assuming that statistical significance necessarily represents clinical improvement.

Accordingly, the Abstract, Results, figure legends, tables/footnotes where appropriate, and Discussion have been revised to ensure that the direction and clinical meaning of the observed changes are accurately reported. We have also removed the previous general statement that both groups improved and replaced it with a more precise description of the between-group differences in outcome trajectories.

We sincerely thank the reviewer for identifying this important interpretive issue, which has helped us improve the accuracy and clarity of the manuscript.

Response to reviewer 4 Comment

Reviewer 4 – Comment 1

Based on Tables 2 and 3, the reported changes in the Neck Disability Index (NDI) and Visual Analog Scale (VAS) scores in the control group appear inconsistent with the interpretation provided in the Results section. I encourage the authors to carefully review the presented values, statistical analyses, and corresponding interpretations to ensure consistency throughout the manuscript.

Response

Thank you for highlighting this important issue. We carefully rechecked the numerical values in Tables 2 and 3, the statistical analyses, and Figures 1 and 2. We agree that the previous interpretation did not accurately reflect the direction of change in the outcome measures.

In particular, higher NDI scores indicate greater disability. Therefore, the increase in NDI scores in the exercise-only control group from 43.69 at baseline to 52.79 at 1 month and 58.82 at 4 months represents worsening disability rather than improvement. We have corrected this interpretation throughout the manuscript and have removed the previous statement that both groups improved in disability.

The VAS results have also been reinterpreted according to the direction of the scale, with lower scores indicating lower pain intensity. The Results, Abstract, Discussion, figure legends, and Conclusion have been revised to ensure that the reported interpretation is consistent with the actual numerical findings and statistical analyses.

Reviewer 4 – Comment 2

Please provide additional information regarding the sample size calculation. It would be helpful to describe how the sample size was determined, including the expected effect size, statistical power, significance level, and the primary outcome used for the calculation.

Response

Thank you for this suggestion. We have expanded the Sample Size Calculation section to provide the requested methodological details. The calculation was based on the Neck Disability Index (NDI) as the primary outcome and now specifies the expected effect size, statistical power, significance level, and the allowance for attrition.

The original calculation required 44 participants, and an anticipated 20% attrition rate was considered, resulting in a final target sample of 56 participants (28 per group).

Reviewer 4 – Comment 3

Although block randomization is mentioned, providing additional details regarding block size, sequence generation, and allocation concealment would improve the methodological transparency of the trial.

Response

We agree with the reviewer. The Randomization and Allocation Concealment section has been expanded to describe the method of sequence generation, block randomization, block size, allocation ratio, and allocation concealment. We have also clarified the roles of the personnel involved in sequence generation, participant enrollment, and treatment assignment, to the extent documented in the study protocol.

Reviewer 4 – Comment 4

Since the study is described as single-blind, it would be useful to specify which individuals were blinded.

Response

Thank you. We have clarified the blinding procedures in the Methods section. The outcome assessor and the statistical analyst were blinded to treatment allocation. Because the intervention involved active mesotherapy injections, the treating physician and participants could not be blinded. This limitation is now explicitly acknowledged in the Discussion.

Reviewer 4 – Comment 5

Both groups received oral medications in addition to exercise therapy. Clarifying the dosage, duration of administration, and the rationale for prescribing these medications would help readers better understand the treatment protocol and its potential influence on the outcomes.

Response

We appreciate this comment. We have added the name, dose, frequency, duration, and rationale for the concomitant oral medication regimen to the Intervention section. The same standardized medication regimen was administered to both groups, which was intended to minimize differences in concomitant treatment and reduce its potential confounding effect on the between-group comparison.

Reviewer 4 – Comment 6

Consider reporting effect sizes and confidence intervals alongside P values to facilitate interpretation of the findings.

Response

We agree. In accordance with the reviewer's recommendation, treatment effect estimates and corresponding 95% confidence intervals have been added to the statistical reporting. The between-group differences in change from baseline for NDI and VAS at the predefined follow-up time points are now reported alongside P values. This provides a more informative assessment of the magnitude and precision of the treatment effects.

Reviewer 4 – Comment 7

Please review the selected keywords. One of the listed keywords ("Pulmonary Rehabilitation") does not appear to be related to the subject of the present study and may require revision.

Response

Thank you for identifying this error. The keyword "Pulmonary Rehabilitation" has been removed because it is unrelated to the present study. The keywords have been revised to better reflect the study population, intervention, and outcome measures.

Reviewer 4 – Comment 8

The Discussion could provide a more balanced interpretation of the findings. Since no significant between-group difference was observed for pain intensity, it would be appropriate to discuss this finding more explicitly and ensure that the conclusions accurately reflect the reported results.

Response

We agree with the reviewer. The Discussion and Conclusion have been revised to explicitly state that no statistically significant between-group difference was observed for pain intensity. We have avoided interpreting within-group improvement as evidence of treatment superiority and have clarified that the findings do not establish a significant superiority of mesotherapy over exercise therapy alone for pain reduction.

Reviewer 4 – Comment 9

The manuscript would be further strengthened by discussing the clinical relevance of the findings. In particular, commenting on whether the observed changes exceeded the

minimal clinically important difference (MCID) would enhance the clinical interpretation of the results.

Response

Thank you for this valuable suggestion. We have added a discussion of the clinical relevance of the observed changes in NDI and VAS and have interpreted the magnitude of change in relation to established minimal clinically important difference (MCID) thresholds, where applicable.

We have also emphasized that statistical significance and clinical significance are distinct concepts. In particular, the increase in NDI observed in the exercise-only group was correctly interpreted as worsening disability, and the absence of a significant between-group difference in pain intensity was considered when interpreting the clinical relevance of the findings.

OPEN PEER REVIEW

Revision (1)

REFEREE : Reviewer

13 Sep 2026

Dear Associate Editor

The authors have made the revisions requested by the reviewer and improved the article.

REFEREE : Reviewer

18 Sep 2026

Dear AE

The responses were ok

REFEREE : Associate Editor

23 Sep 2026

Dear EIC

In my opinion, the article has been accepted for publication in MEJRHS. We hope to receive the other qualified articles from that group.

Fatemeh Ehsani-EIC : EIC

23 Sep 2026

Dear Authors

We are pleased to inform you that your article is accepted for publication in the MEJRHS. We hope to receive other qualified articles from your group.