REVIEWER'S REPORT

Manuscript No.: IJAR-55752

Title: Overnight Occlusive Topical Application of High-Concentration 35 kDa Hyaluronic Acid Fragments for Facial Erythema and Subcutaneous Fat: A Case Series,

Recommendation:

Accept as it is …………………………….

Accept after minor revision………………

Accept after major revision ……YES…………

Do not accept (*Reasons below*) ………

Rating	Excel.	Good	Fair	Poor
Originality		√		
Techn. Quality		√		
Clarity		√		
Significance		√		

Reviewer Name: Prof. Dr Dillip Kumar Mohapatra

Detailed Reviewer's Report

The manuscript titled:

"Overnight Occlusive Topical Application of High-Concentration 35 kDa Hyaluronic Acid Fragments for Facial Erythema and Subcutaneous Fat: A Case Series."

1. Strengths

Novelty / Innovation:

Explores the use of **low-molecular-weight (35 kDa) HA fragments** in a **topical occlusive formulation**, which is less studied for facial fat modulation and erythema.

Leverages **biological insights from naked mole rats** to justify translational relevance.

Rapid Observed Effects:

The study demonstrates **visible improvements after a single application**, suggesting potential fast-acting aesthetic and anti-inflammatory effects.

Safety and Tolerability:

No adverse local or systemic effects were reported.

Non-invasive intervention offers a potential alternative to steroids or injectable procedures.

Clear Presentation of Data:

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Tables and figures summarize **quantitative NRS scores** for multiple facial parameters.

Multiple outcome parameters (subcutaneous fat, erythema, skin radiance, pore size) are included, giving a **broad picture of treatment effects**.

Mechanistic Discussion:

Authors attempt to explain effects through **hydration, neuro-inflammatory signaling, and microcirculation modulation**, which strengthens the biological rationale.

2. Weaknesses / Limitations

Sample Size:

Only **5 participants**, which severely limits generalizability and statistical power.

Lack of **control group** prevents assessment of placebo effect or natural variability.

Study Design:

Case series design is inherently exploratory; cannot establish causation.

Occlusive application may **artificially enhance hydration**, potentially confounding results.

Outcome Measures:

Primarily **subjective NRS scoring**, with **no objective imaging (e.g., ultrasound, MRI)** or biochemical markers to validate fat reduction or inflammation attenuation.

Short follow-up period: only **5 applications over 10 days**; long-term efficacy and durability unknown.

Potential Bias:

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Participants were aware of treatment (no blinding).

Small, non-randomized cohort may introduce **selection bias**.

Incomplete Mechanistic Evidence:

Hypotheses about TRP channels and HA fragment signaling are **not directly tested**.

Claims of fat modulation are speculative without tissue-level assessment.

Limited Literature Context:

Most references are animal studies or prior in-house patents; **lack of broader clinical trials** or comparable topical HA studies in humans.

Reference [5] ("in press") may not yet be publicly accessible, limiting reproducibility.

3. Significance / Impact

Potential clinical significance:

Introduces a **non-invasive, safe, topical approach** for facial aesthetic concerns (erythema, subcutaneous fat, pores).

If validated in larger trials, could reduce reliance on **steroids, injections, or invasive procedures**.

Scientific interest:

Builds a bridge between **naked mole rat biology** and **human skin treatment**.

Adds to growing interest in **molecular-weight-specific HA fragments** for dermatological applications.

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Limitations to impact:

Small-scale exploratory data; impact is **preliminary** and cannot yet influence clinical practice.

4. Key Points / Reviewer Summary

Novelty: Use of 35 kDa HA fragments in overnight occlusive application for **rapid reduction of facial erythema and subcutaneous fat**.

Effectiveness: All 5 participants reported **visible improvement**, with NRS scores showing decreases in fat thickness, erythema, pore size, and improved skin radiance.

Safety: No adverse events reported.

Mechanistic Insight: Effects possibly related to **hydration, microcirculation, and neuro-inflammatory signaling**, inspired by naked mole rat HA biology.

Limitations:

Small, uncontrolled, non-randomized case series.

Subjective measures only; no objective validation.

Short duration; uncertain long-term effects.

Future Directions:

Larger, randomized controlled trials with **objective imaging and biomarkers**.

Compare occlusive vs. non-occlusive application.

Investigate underlying **molecular and cellular mechanisms**.

Reviewer Recommendation:

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Accept with Major Revisions for Publication (in peer-reviewed journal):

Authors should **highlight limitations clearly**, avoid overgeneralizing, and propose **objective follow-up studies**.

Add discussion on **occlusion confounding effects** and potential placebo impact.

WHY MAJOR REVISION

1. Title & Abstract

Observation:

Title clearly states intervention (35 kDa HA fragments, overnight occlusive application) and outcome (facial erythema, subcutaneous fat).

Abstract reports positive outcomes with all participants showing improvement.

Reason for Revision:

Abstract **overstates efficacy**: "rapid improvements" and "well tolerated" are based on **only 5 participants** without controls.

Needs **cautious language**: e.g., "preliminary findings suggest potential improvement" instead of definitive statements.

Abstract **lacks mention of limitations** (sample size, subjective outcome, short duration).

Justification: Overstatement may mislead readers; reviewers often request careful phrasing.

2. Introduction

Observation:

Provides **biological rationale** linking naked mole rat HA to human facial fat and inflammation.

Discusses molecular weight–specific HA fragment activity.

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Reason for Revision:

Some statements **overgeneralize animal findings to humans**.

References are partly **patents and "in press" publications** — not peer-reviewed, limiting credibility.

Needs **clearer gap statement**: why topical 35 kDa HA is clinically important and what is unknown.

Justification: Journals expect **strong literature context and proper evidence for claims**, especially when translating from animal models.

3. Methods – Participants

Observation:

Five participants, aged 27–68, Asian, described individually.

Excluded recent facial treatments.

Reason for Revision:

Sample size extremely small, limits generalizability.

No control group — cannot distinguish placebo effect from treatment.

Selection criteria unclear: why only 5 participants, rationale for age range, gender distribution, and ethnicity.

Justification: Reviewers will note **lack of statistical power and risk of bias**, requiring clarification.

4. Methods – Intervention

Observation:

10% 35 kDa HA, overnight occlusive application, every 2 days ×5.

Reason for Revision:

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Occlusion itself may alter skin hydration or inflammatory response, potentially confounding results.

No rationale for dosage or frequency — why 10%? why every 2 days?

Product code given – may raise concern for bias or commercial influence.

Justification: Needs explanation of choice of formulation and mitigation of confounding effects.

5. Methods – Outcome Assessment

Observation:

Used 0–10 NRS for subcutaneous fat, erythema, radiance, pore size.

Reason for Revision:

All subjective measures — prone to bias.

No objective validation (ultrasound, skin imaging, biochemical markers).

Short-term assessment (after 5 applications only).

Justification: Reviewers typically request **objective measures or acknowledgment of subjective limitation**.

6. Results

Observation

All participants showed improvements.

Statistical significance indicated, but small n.

Reason for Revision:

Statistical analysis is limited: small sample cannot provide meaningful p-values.

Table suggests **high precision (SD ±0.5)** with only 5 subjects — misleading.

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No reporting of individual variability beyond averages.

Justification: Risk of **overinterpreting trends in a tiny cohort**. Requires rewording and transparency.

7. Discussion

Observation:

Mechanistic reasoning (hydration, TRP channels) is provided.

Links to naked mole rat biology and HA function.

Reason for Revision:

Mechanisms are **speculative**, not experimentally validated.

Overemphasizes rapid effects without **acknowledging alternative explanations** (occlusion, placebo, observer bias).

Comparisons to steroids are made, but no **direct comparative study** performed.

Justification: Needs **more cautious interpretation**, clearly stating hypothesis vs. proven mechanism.

8. Limitations

Observation

Authors mention small sample, subjective NRS, occlusion confounding.

Reason for Revision:

Limitations acknowledged but **downplayed**..

Should explicitly note: **no control group, short follow-up, lack of objective validation**, and **possible placebo effects**.

Justification: Journals expect **transparent limitations** for credibility.

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9. Conclusion

Observation:

States "rapid onset," "good tolerability," and "potentially effective."

Reason for Revision:

Overly confident for a **5-person exploratory case series**.

Should rephrase: "preliminary evidence suggests potential… requiring confirmation in controlled studies."

Justification: Must **align conclusion with study design and evidence level**.

Summary – Why Major Revisions

Overstatement of efficacy → must be tempered for small exploratory cohort.

Sample size and design limitations → tiny, uncontrolled study, subjective outcomes, short follow-up.

Mechanistic claims → speculative, not experimentally validated.

Potential bias/confounding → occlusion effect, selection bias, commercial product use.

Statistical and reporting concerns → precision/p-values misleading given n=5.

References → reliance on in-house patents, unpublished, or "in press" studies.

In short: the manuscript is **interesting and novel**, but its **design and data interpretation require major revisions** before it could be considered for publication. Minor edits (language or formatting) would not address the fundamental issues.