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Comparative Efficacy and Recurrence Risk of Intralesional Therapies for Hypertrophic Scars and Keloids: A Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 July 2025 and was last updated on 2 July 2025.

INTRODUCTION

Review question / Objective This systematic review and network meta-analysis aims to compare the efficacy and recurrence rates of commonly used intralesional pharmacologic treatments for hypertrophic scars and keloids, in order to establish a relative ranking of interventions based on currently available randomized controlled trial evidence.

Review question:
Among patients with hypertrophic scars or keloids, which intralesional pharmacologic treatments are most effective in reducing scar severity, and which are associated with the lowest recurrence rates?

PICOS framework:
1. Population: Individuals of any age or sex with clinically diagnosed hypertrophic scars or keloids, regardless of anatomical location or etiology.
2. Intervention: Intralesional injection of pharmacologic agents including triamcinolone acetonide, 5-fluorouracil, bleomycin, verapamil, botulinum toxin A, and their combinations.
3. Comparator: Other intralesional treatments or standard care, including head-to-head comparisons or indirect comparisons across studies.
4. Outcomes:
– Primary outcome: Effective rate, defined as ≥50% clinical improvement or author-defined categorical response.
– Secondary outcome: Recurrence rate, defined as return of scar symptoms or regrowth following initial response.
5. Study design: Only randomized controlled trials (RCTs) will be included.

Rationale Hypertrophic scars and keloids are fibroproliferative skin disorders that result from abnormal wound healing. They often lead to cosmetic disfigurement, physical discomfort, and

psychosocial distress. Intralesional pharmacologic therapy is commonly used for these conditions, but the comparative effectiveness and durability of different agents remain unclear. Existing systematic reviews are mostly limited to pairwise comparisons, and many lack head-to-head evidence across multiple treatments. In addition, variability in outcome definitions and methodological quality has contributed to inconsistent findings in the literature. Recurrence, which is a key clinical concern, has often been underreported or insufficiently analyzed in previous studies. With the increasing use of combination therapies and newer intralesional agents, there is a pressing need for a comprehensive synthesis of high-quality evidence. This review aims to include only randomized controlled trials with extractable dichotomous outcomes, allowing for a robust network meta-analysis. The goal is to establish a reliable treatment ranking that can guide clinical practice and support individualized management for patients with hypertrophic scars and keloids.

Condition being studied Hypertrophic scars and keloids are types of pathological scars that arise from abnormal wound healing. Both conditions are characterized by excessive fibroblast proliferation and extracellular matrix deposition, leading to raised, firm, and often symptomatic lesions. While hypertrophic scars remain confined to the original wound boundary and may regress over time, keloids extend beyond the initial injury site and tend to persist or enlarge. These lesions commonly result from trauma, burns, surgery, or inflammatory skin diseases. Patients may experience pain, itching, restricted mobility, and psychological distress, making effective treatment a clinical priority.

METHODS

Search strategy The search strategy combined MeSH terms and keywords related to pathological scars and intralesional therapies. The following search terms were used: ("keloid" OR "hypertrophic scar") AND ("intralesional" OR "injection") AND ("triamcinolone" OR "5-fluorouracil" OR "verapamil" OR "bleomycin" OR "botulinum toxin" OR "interferon" OR "vitamin D" OR "platelet-rich plasma" OR "PRP" OR "betamethasone" OR "corticosteroid" OR "steroid").

Participant or population The review will include human participants of any age, sex, or ethnicity who have been clinically diagnosed with hypertrophic scars or keloids. Diagnosis must be based on physical examination or standardized clinical criteria as reported in the original studies. Studies involving scars of any anatomical location and of any etiology (e.g., post-surgical, post-traumatic, or post-inflammatory) will be considered eligible. There will be no restrictions on the duration of the scar or prior treatments received. Non-human studies, in vitro studies, and studies involving healthy volunteers will be excluded.

Intervention The interventions of interest are intralesional pharmacologic treatments administered for the management of hypertrophic scars and keloids. These include monotherapy or combination therapy involving agents such as triamcinolone acetonide (a corticosteroid), 5-fluorouracil (a cytotoxic agent), bleomycin (an antitumor antibiotic), verapamil (a calcium channel blocker), and botulinum toxin A (a neuromodulator). All interventions must be delivered via intralesional injection, with or without adjunctive local anesthesia. Studies assessing the efficacy of these agents as standalone or in combination with one another will be included. Non-injectable forms (e.g., topical, oral, or systemic) or surgical/laser-based treatments without pharmacologic injection will be excluded.

Comparator Comparative interventions include other intralesional pharmacologic treatments evaluated in head-to-head trials or through indirect comparisons within a network meta-analysis framework. These may involve comparisons between different monotherapies (e.g., triamcinolone acetonide vs. 5-fluorouracil), combination therapies (e.g., triamcinolone plus 5-fluorouracil), or standard care. Placebo or no-treatment arms will also be included if available in eligible randomized controlled trials. The purpose of these comparisons is to assess the relative effectiveness and recurrence profiles of each intervention.

Study designs to be included This review will include only randomized controlled trials (RCTs) that evaluate the efficacy and/or recurrence outcomes of intralesional pharmacologic treatments for hypertrophic scars and keloids. Both parallel-group and split-scar RCT designs will be eligible for inclusion, provided that they offer extractable dichotomous outcome data. Non-randomized studies, observational studies, case series, case reports, conference abstracts without full data, and in vitro or animal studies will be excluded.

Eligibility criteria There will be no language or publication date restrictions. Full-text articles must be available for review. Studies must report

extractable dichotomous outcomes for either the effective rate or recurrence rate; trials that report only continuous outcomes without convertible thresholds will be excluded. Trials that combine intralesional pharmacologic therapy with surgical, laser, or other non-pharmacologic interventions, where the specific contribution of the pharmacologic agent cannot be isolated, will also be excluded. Studies published as abstracts without sufficient data for extraction, duplicate publications, non-English articles, and protocols without results will not be included.

Information sources Electronic databases including PubMed, Embase (via Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science will be systematically searched from inception to May 2025. Additionally, ClinicalTrials.gov will be searched to identify ongoing or unpublished trials. Reference lists of included studies and relevant systematic reviews will be manually screened for additional eligible articles. When outcome data are missing or unclear, corresponding authors will be contacted to obtain necessary information. No language restrictions will be applied.

Main outcome(s) 1. Effective rate
This is defined as the proportion of patients achieving clinically significant improvement following treatment. Improvement is typically defined as ≥50% reduction in lesion size, ≥50% improvement in Vancouver Scar Scale (VSS) or comparable clinical assessment criteria, as reported by each included trial. Studies must report dichotomous outcomes or provide data that can be converted to binary format. Outcome timing varies across studies but generally ranges from 4 to 12 weeks after the final treatment session. The effect measure used for synthesis will be the odds ratio (OR) with 95% confidence interval (CI).
2. Recurrence rate
This refers to the proportion of patients whose hypertrophic scar or keloid recurs after initial improvement, based on clinical reassessment at follow-up. Recurrence may be defined by scar regrowth, return of symptoms, or worsening of previously improved lesions. The follow-up duration varies among studies, typically ranging from 3 to 12 months. The effect measure used will be the odds ratio (OR) with 95% confidence interval (CI).

Additional outcome(s) No additional outcomes will be assessed in this review.

Data management All retrieved records from database searches will be imported into reference management software (EndNote X9) for deduplication. Title and abstract screening, followed by full-text eligibility assessment, will be performed using Microsoft Excel with predefined inclusion and exclusion criteria. A standardized data extraction form will be used to collect relevant variables, including study characteristics, intervention details, outcome measures, and follow-up duration. Two reviewers will independently extract and verify data. Discrepancies will be resolved through discussion or consultation with a third reviewer. Final datasets will be stored securely on password-protected institutional computers.

Quality assessment / Risk of bias analysis The risk of bias of included randomized controlled trials will be independently assessed by two reviewers using the Cochrane Risk of Bias 2.0 (RoB 2) tool. This tool evaluates five domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. Each domain will be judged as "low risk," "some concerns," or "high risk," and an overall risk-of-bias judgment will be assigned accordingly. Any disagreements will be resolved through discussion or by consulting a third reviewer. Results will be presented in tabular and graphical formats.

Strategy of data synthesis A network meta-analysis will be conducted using a frequentist random-effects model to synthesize both direct and indirect comparisons across eligible interventions. Statistical analyses will be performed using the netmeta R package (version 2.9-0) through the MetaInsight web-based platform (version 6.4.0). Dichotomous outcomes (effective rate and recurrence rate) will be pooled and reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Treatment ranking will be established using the surface under the cumulative ranking curve (SUCRA) values. Network geometry will be visualized to assess the structure and connectivity of available comparisons. Heterogeneity will be assessed using the tau-squared (τ^2) statistic. Global inconsistency will be examined using the design-by-treatment interaction model, and local inconsistency will be evaluated through loop-specific inconsistency tests. Sensitivity analyses will be conducted where appropriate. All decisions regarding data synthesis will follow PRISMA-NMA guidelines.

Subgroup analysis No subgroup analyses are planned for this review. This decision is based on the substantial heterogeneity in the design and reporting of the included randomized controlled trials. Most studies lacked consistent stratification by variables such as anatomical site, lesion duration, patient age, or treatment frequency, and did not provide sufficient data to support subgroup-level comparisons. Additionally, the number of trials available for each individual treatment node is limited, reducing the statistical power and interpretability of any potential subgroup analyses. To maintain methodological rigor and avoid overinterpretation of sparse data, no predefined subgroup analyses will be conducted. The review will focus on overall treatment effects derived from the full network.

Sensitivity analysis No sensitivity analyses are planned for this review.
This decision is based on the limited number of eligible randomized controlled trials available for each treatment comparison within the network. Many of the included studies are small in size and vary in outcome definitions and follow-up durations, making it difficult to identify a consistent subset of studies suitable for sensitivity testing. In addition, there is insufficient granularity in the reporting of study-level characteristics (e.g., risk of bias, treatment dose, or lesion chronicity) to support stratified re-analyses. Given these constraints, performing sensitivity analyses may yield misleading or inconclusive results. Therefore, the review will focus on reporting the overall network estimates using all eligible studies, while acknowledging these limitations in the interpretation of findings.

Language restriction This review will include only studies published in English. Non-English articles will be excluded due to limitations in translation resources and to ensure consistency in data interpretation and quality assessment.

Country(ies) involved Taiwan.

Keywords keloid; hypertrophic scar; intralesional injection; triamcinolone acetonide; 5-fluorouracil; bleomycin; verapamil; botulinum toxin A; randomized controlled trial; network meta-analysis; efficacy; recurrence.

Contributions of each author
Author 1 - I-Chang Lai - Author 1 conceptualized the review topic, conducted the systematic database search, performed the risk of bias assessment, organized and synthesized the extracted data, prepared all tables and figures, drafted the initial manuscript, ensured compliance with journal formatting requirements, and will oversee the submission process.
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Author 2 - Guan-Lun Huang - Author 2 participated in the database search, contributed to data extraction, assisted in drafting the manuscript, and reviewed the formatting and structure of the final version.
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Author 3 - Kuan-Chun Lee - Author 3 assisted in the risk of bias assessment using the RoB 2 tool, contributed to the drafting of the manuscript, and supported the preparation and refinement of tables and figures. The author also participated in the formatting and structural organization of the final version.Author 3 assisted with the risk.
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