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Review

Efficacy of emerging therapies versus traditional therapies in the treatment of hypertrophic scars and keloids: A systematic review

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Abstract. *Introduction:* Hypertrophic scars and keloids are abnormal wound-healing alterations that disproportionately affect populations of African, Asian, and Latin descent. Traditional therapies, such as surgery, corticosteroids, and laser treatments, demonstrate limited effectiveness and frequent recurrence. Emerging therapies, including mesenchymal stem cells and growth factors, hold promise for improved inflammatory regulation and tissue remodeling. *Objective:* To compare the efficacy and safety of emerging therapies versus traditional treatments in reducing hypertrophic scars and keloids, evaluating aesthetic outcomes, scar size, and recurrence rates. *Methods:* A systematic review was conducted in accordance with PRISMA guidelines, including 8 studies with 525 participants. The interventions assessed comprised mesenchymal stem cells, platelet-rich plasma, and triamcinolone-laser combinations. Primary outcomes were volume reduction, aesthetic improvement, and decreased recurrence. *Results:* Emerging therapies, such as platelet-rich plasma, showed significant reductions in the Vancouver Scar Scale ($p<0.05$) and decreased profibrotic markers such as CTGF (40%-50% reduction). Traditional treatments, like intralesional triamcinolone, achieved an average scar volume reduction of 90.1% within one year ($p=0.031$) but were associated with greater adverse effects, such as hypopigmentation. Combined therapies offered improved aesthetic results with a lower incidence of side effects. *Discussion:* Emerging therapies demonstrate significant potential, particularly in reducing profibrotic factors and achieving an initial aesthetic improvement. However, they present limitations regarding standardization and long-term sustainability. Traditional therapies, while effective, require combinations to minimize recurrence and adverse effects.

Key words: Hypertrophic scars, Keloids, Regenerative therapies, Mesenchymal stem cells, Platelet-rich plasma

Introduction

Hypertrophic scars and keloids represent a significant clinical challenge due to their abnormal nature within the wound-healing process. Unlike normal scars, these lesions arise from an imbalance in tissue remodeling mechanisms, leading to excessive growth of the extracellular matrix and fibroblasts. This phenomenon is associated with genetic, racial, and environmental factors, more frequently affecting individuals of African, Asian, and Latin descent[1,2]. Hypertrophic scars, although generally confined to the original site of injury, are characterized by being elevated, rigid, and often pruritic. On the other hand, keloids not only

grow beyond the boundaries of the initial lesion but are also more persistent and resistant to conventional treatments[1,2].

Traditional therapeutic strategies include surgical approaches, intralesional corticosteroids, and laser therapy. While effective in removing excess scar tissue, surgery is associated with high recurrence rates, particularly if not combined with other therapeutic modalities. Intralesional steroids, in turn, have proven effective in reducing the size and consistency of scars, but their prolonged use may lead to adverse effects, such as skin atrophy or hypopigmentation. Likewise, laser therapies have shown improvements in scar color and texture, although their ability to prevent recurrences remains limited and depends on the type of laser and therapeutic regimen used[3].

In contrast, emerging therapies have focused on the use of biological and regenerative tools, such as mesenchymal stem cells and platelet-derived growth factors. These interventions aim not only to repair existing damage but also to regulate inflammatory and tissue remodeling processes, promoting a more physiological environment for healing. Despite their promising potential, these strategies are in the early stages of clinical research, and their implementation still faces technical, regulatory, and economic limitations[3].

Although traditional treatments have been widely investigated and applied, there is an urgent need for comparative evaluations to determine their relative efficacy against emerging therapies. Available studies on surgery, steroids, and lasers, generally address individual outcomes, such as scar size reduction or aesthetic improvements, without considering their overall impact on recurrence or patient quality of life. Furthermore, these treatments present variability in outcomes depending on factors such as the technique employed, operator expertise, and scar characteristics[1,2].

On the other hand, although emerging therapies such as stem cells and growth factors have demonstrated positive effects in preclinical models and pilot studies, their long-term efficacy and safety are not fully validated. The lack of standardization in application protocols, variability in stem cell sources, and difficulty in measuring uniform outcomes complicate the assessment of their real impact. Moreover, the evidence supporting these interventions is primarily based on case studies or small cohorts, limiting the generalizability of their findings[3].

The absence of systematic studies directly comparing traditional treatments with emerging therapies constitutes a critical gap in the literature. This lack of data prevents clinicians from making evidence-based decisions and limits the development of clinical practice guidelines to optimize the management of hypertrophic scars and keloids. Therefore, a comprehensive evaluation is required that incorporates not only clinical aspects but also cost-effectiveness and patient satisfaction perspectives, which are essential for advancing toward a more integrated and personalized management approach.

In this context, we hypothesize that emerging therapies, such as the use of stem cells and growth factors, are more effective than traditional therapies in reducing scar size, improving aesthetics, and decreasing recurrence. The present systematic review aims to evaluate and synthesize the available evidence on the efficacy of these interventions, directly comparing their clinical outcomes in terms of the aforementioned key variables.

To address this issue, we will conduct a systematic review of the literature, following PRISMA guidelines, to identify and analyze relevant studies comparing emerging and traditional therapies in the management of hypertrophic scars and keloids. This analysis will not only help clarify the relative superiority of these therapeutic strategies but also provide an evidence-based framework to guide clinical practice and future research in the field of pathological wound healing.

Methods

Study design

A systematic review of the literature was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, evaluating clinical studies that compared emerging therapies (stem cells, growth factors) with traditional therapies (surgery, laser, steroids) for hypertrophic scars and keloids.

Selection criteria

Types of studies

Randomized controlled trials (RCTs), non-randomized controlled studies, and observational studies (cohort and case-control studies) published in English and Spanish were included. Single case studies, narrative reviews, and articles without full-text access were excluded.

Types of participants

Studies including patients diagnosed with hypertrophic scars or keloids, regardless of age, sex, or comorbidities, were selected.

Types of interventions/exposures

- **Emerging interventions:** Therapies based on stem cells and growth factors.
- **Comparative interventions:** Traditional treatments, including surgery, laser therapy, and steroids.

Types of outcomes

- **Primary Outcomes:**
  - Reduction in scar size measured in terms of volume, area, or thickness.
- **Secondary Outcomes:**
  - Aesthetic improvement assessed using validated scales (e.g., Vancouver Scar Scale).
  - Reduction in recurrence documented through clinical follow-up.

Search methods for study identification

Electronic searches

Searches were conducted in the following databases:

- PubMed/MEDLINE
- Embase
- Cochrane Library
- Scopus
- Web of Science

Search terms included keywords and MeSH terms related to "emerging therapies," "traditional therapies," "hypertrophic scars," "keloids," and "clinical efficacy."

Other resource searches

The reference lists of selected studies were reviewed to identify relevant works not captured in the initial searches. Additionally, a manual search of conference proceedings and gray literature was performed on platforms such as OpenGrey.

Data collection and analysis

Study selection

Two independent reviewers screened the titles and abstracts of retrieved studies to determine eligibility. Disagreements were resolved by a third reviewer.

Data extraction and management

A standardized form was designed to extract relevant information, including study characteristics, number of participants, interventions, outcomes, and main results.

Critical appraisal of studies using epidemiological design assessment tools

The quality of the studies was assessed using:

- The Cochrane Risk of Bias Tool for randomized trials.
- The ROBIS instrument for systematic reviews.

Results

A total of 12,495 references were identified through electronic database searches. After removing 2,952 duplicate records, 9,543 records were screened

during the initial screening phase. Of these, 9,509 records were excluded for not meeting the inclusion criteria.

Subsequently, 34 documents were selected for a full-text evaluation; however, 4 of these could not be retrieved. Ultimately, 30 full-text articles were assessed, of which 26 were excluded due to different populations (n = 8) or different interventions (n = 18).

In the end, 8 studies were included in the review. The PRISMA flow diagram shows the results of the study selection and screening process (see Figure 1).

Characteristics Of the studies

Six studies were included in the review, with a total of 525 participants. The studies were conducted in different countries: two in Iran[4,5], one in Thailand[6], one in Egypt[7], one in China[8], and one in the Netherlands[9].

Five of the included studies were clinical trials[4,6-9], while one was a systematic review of regenerative medicine treatments[5]. The clinical trials evaluated diverse interventions, including combinations of intralesional injections, fractional lasers, platelet-rich plasma

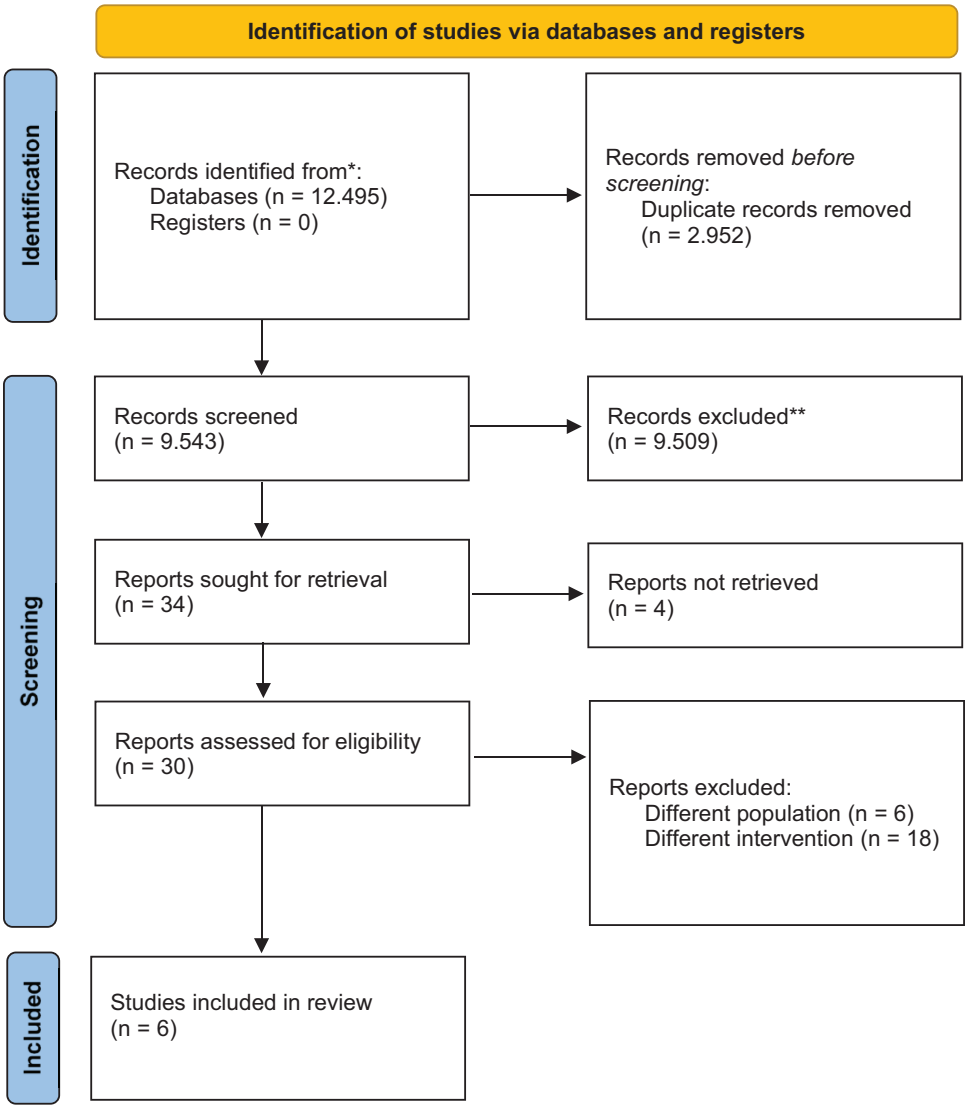

Figure 1. PRISMA Flow Diagram.

(PRP), botulinum toxin type A (BTX-A), mesenchymal stem cells (MSCs), and stromal vascular fractions (SVF). The sample sizes for the clinical trials ranged from 22 to 60 participants, while the systematic review included data from 377 patients collected from 8 previous studies.

The timeframes varied significantly among studies, ranging from short-term assessments of 24 hours[8] to follow-ups of 12 months[9]. Most participants were adults with hypertrophic scars or keloids, excluding individuals with systemic diseases, pregnant women, and minors. Notably, one study focused on female patients undergoing breast reduction surgery[9], while another was based on the use of in vitro cell lines[8].

The methodological approaches and participant characteristics are described in Table 1.

Risk Of bias assessment

The risk of bias assessment of the included studies is summarized in Table 2. The main assessed characteristics are described below:

Generation and concealment of the randomization sequence

All studies used appropriate methods for random sequence generation, as reflected in their methodological designs (low risk of bias). However, three studies[4,6,8] did not clearly report allocation concealment prior to enrollment, which was classified as an unclear risk of bias.

Blinding of participants and personnel

Differences in blinding were identified among the studies. Two studies[7,9] achieved complete participant blinding, while in the others[4,6,8], participants were aware of the assigned intervention, increasing the risk of performance bias.

Outcome assessment and analysis

Five studies reported appropriate data analysis consistent with prespecified analytical plans (low risk of bias). Furthermore, in all cases, the methods used to measure outcomes were adequate, with no evidence of differential measurement bias between intervention groups.

Missing data

Although some studies did not report complete data for all participants[4,6], there was no evidence that missing data influenced the reported outcomes, minimizing the risk of attrition bias.

Reporting bias

Four studies[6-9] reported all prespecified outcomes in their methods, which was considered low risk of reporting bias. However, in the case of Zahra et al., 2023, uncertainty existed regarding the selection of the reported numerical outcome, leading to an unclear risk of reporting bias.

Overall assessment

In general, three studies[7-9] were classified as having a low risk of bias, while the other two[4,6] exhibited a moderate risk of bias due to limitations in allocation concealment and participant blinding.

The risk of bias assessment for the systematic review conducted by Alireza et al. is summarized as follows[5]:

Domain 1: Study Eligibility Criteria: The review met prespecified and appropriate eligibility criteria aligned with the research question, which were unambiguous and justified. No significant concerns were identified in this domain, which was therefore considered at low risk of bias.

Domain 2: Study Identification and Selection**:** The authors used an appropriate range of electronic databases and additional methods to identify relevant reports. While the search strategies and restrictions were appropriate, efforts to minimize selection errors were classified as "probably yes," introducing some uncertainty. Nonetheless, this domain was still considered low risk of bias.

Domain 3: Data Collection and Study Assessment**:** Although relevant data were collected

Table 1. Characteristics of Included Studies

Author	Year	Country	Design	Objective	N	Characteristics	Time Horizon
Zahra, et al (4)	2023	Iran	Clinical trial	Compare the efficacy of intralesional triamcinolone alone versus triamcinolone combined with verapamil in the treatment of postoperative keloids.	32	Adults aged 18–50 years with postoperative keloids between 3 and 12 months old and sizes ranging from 0.5 to 10 cm.	Treatment with injections every 3 weeks up to 8 sessions; follow-up 3 months after the last injection.
Niti, et al (6)	2022	Thailand	Clinical trial	Compare the therapeutic effect of fractional CO_2 laser combined with topical triamcinolone (TA) versus intralesional triamcinolone in the treatment of keloids.	22	Adults with keloids; excluded pregnant patients, herpes zoster infections, immunocompromised individuals, skin diseases, or steroid/lidocaine allergies.	1 year of treatment with follow-up every 2 months.
Yomna, et al (7)	2021	Egypt	Clinical trial	Compare the therapeutic efficacy and safety of intralesional injections of botulinum toxin type A (BTX-A), platelet-rich plasma (PRP), and triamcinolone acetonide (TAC) in the treatment of keloids.	60	Patients with newly diagnosed, stable, and untreated keloids of less than 6 months duration; excluded patients with systemic or dermatologic diseases, pregnant or breastfeeding women, and children under 12.	Evaluations after each session and at the end of the follow-up period (3 sessions total, every 4 weeks).
Fengjun, et al (8)	2016	China	Clinical trial	Investigate the paracrine effects of bone marrow-derived mesenchymal stem cells (BMSCs) on the biological behavior of fibroblasts from hypertrophic scars and keloids.	-	Fibroblasts derived from hypertrophic scars, keloids, mature scars, and normal skin, obtained from patients with surgical scars.	Evaluations at 24–60 hours for proliferation and migration, and 48 hours for gene and protein expression.
Joris, et al (9)	2022	Netherlands	Clinical trial	Evaluate whether adipose tissue stromal vascular fraction (tSVF) can reduce scar formation after surgery.	40	Women aged 18–60 years undergoing breast reduction surgery. Excluded those with conditions such as systemic diseases affecting wound healing, cancer history, hormonal therapy, smoking, among others.	Follow-up at 6 and 12 months.
Alireza, et al (5)	2024	Iran	Systematic review	Examine the efficacy, safety, and satisfaction of regenerative medicine treatments for hypertrophic scars and keloids.	377 (from 8 included studies)	191 women, 146 men, mean age 31.4 years; hypertrophic scars (37.5%) and keloids (62.5%).	1 to 6 months.

Table 2. Risk of Bias Assessment of Included Clinical Trials

Question	Zahra, et al (4)	Niti, et al (6)	Yomna, et al (7)	Fengjun, et al (8)	Joris, et al (9)
1.1 Was the allocation sequence random?	Y	Y	Y	Y	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned?	PY	PY	Y	PY	Y
1.3 Did baseline differences between intervention groups suggest a problem with randomization?	N	N	N	N	N
2.1 Were participants aware of their assigned intervention during the trial?	Y	Y	N	N	N
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	Y	PY	PY	PY
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	NI	N	N	N	N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA	NA	NA	NA
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA	NA	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	Y	Y	Y	Y
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	PY	PY	PY	PY
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N	PY	Y	Y	Y
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	N	N	N	N
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA	NA	NA	NA
4.1 Was the method of measuring the outcome inappropriate?	N	N	N	N	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	N	N	N	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Y	Y	PY	Y	Y

Table 2 (*continued*)

Question	Zahra, et al (4)	Niti, et al (6)	Yomna, et al (7)	Fengjun, et al (8)	Joris, et al (9)
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Y	Y	PY	PY
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA	NA	NA	NA
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Y	Y	Y	Y
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements within the outcome domain?	PY	N	Y	Y	Y
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N	N	N	N	N

Table 3. Results of Included Studies

Author	Design	Intervention	Comparator	Outcomes	Results
Zahra, et al (4)	Clinical trial	Intralesional triamcinolone and verapamil (VT group)	Intralesional triamcinolone alone (T group)	Vancouver Scar Scale (VSS), flexibility, height, width, length, pigmentation, local and systemic adverse effects	**Scar length (cm)**: VT group (baseline: 5.6 ± 3; final: 3 ± 2.3; p<0.001), T group (baseline: 6.9 ± 3.2; final: 3.7 ± 2.4; p<0.001). **Scar width (cm)**: VT group (baseline: 6.31 ± 2.9; final: 2.1 ± 1.4; p<0.004), T group (baseline: 6.5 ± 1.9; final: 2.4 ± 1.3; p<0.001). **Scar height (mm)**: VT group (baseline: 4.5 ± 1.2; final: 0.1 ± 0.5; p<0.001), T group (baseline: 4.3 ± 1; final: 0.3 ± 0.7; p<0.001). **Scar flexibility (0-5 scale)**: VT group (baseline: 3 ± 0.9; final: 0.5 ± 0.6; p<0.001), T group (baseline: 2.7 ± 1.1; final: 1 ± 0.2; p<0.001). **Pigmentation (0-3 scale)**: VT group (baseline: 1.9 ± 0.2; final: 0.1 ± 0.3; p<0.001), T group (baseline: 2 ± 0; final: 1.1 ± 0.9; p=0.227). **VSS Score**: VT group (baseline: 8.8 ± 2; final: 1.5 ± 0.6; p<0.001), T group (baseline: 9 ± 1.8; final: 4.1 ± 1.9; p<0.01). **Adverse effects**: VT group reported fewer adverse effects (n=3, 18.7%) compared to T group (n=7, 43.7%), including atrophy (T group: 25%), hypopigmentation (12.5%), and ulceration (6.2%).
Niti, et al (6)	Clinical trial	Group A: Fractional CO_2 laser + topical triamcinolone (TA)	Group B: Intralesional triamcinolone (TA) alone	Scar volume, Vancouver Scar Scale (VSS), recurrence rates, pain scores, adverse events	**Scar volume:** Group A: mean volume reduction from 5608.4 ± 7251.0 mm^3 to 2744.3 ± 5619.3 mm^3 (p<0.001); Group B: volume reduction from 3944.8 ± 4368.6 mm^3 to 286.6 ± 412.9 mm^3 (p<0.001). Reduction was faster in Group B at 2 months versus 4 months in Group A. Final volume change: Group A: 59.1%, Group B: 86.5% (p=0.016). Final reduction after 1-year follow-up: Group A: 64.8%, Group B: 90.1% (p=0.031). **VSS Score:** Group A: reduction from 8.0 ± 1.5 to 4.8 ± 1.6 (p<0.001); Group B: reduction from 8.4 ± 0.8 to 4.8 ± 1.6 (p<0.001). No significant difference between groups at 12 months (p=1.000). **Recurrence:** Resolution at 1 year: Group A: 63.6% (7/11); Group B: 72.7% (8/11). Recurrence: Group A: 9.1%, Group B: 18.2%. Partial reduction (<50%) in Group A: 27.3%, Group B: 9.1%. **Pain:** Mean VAS pain score: Group A: 1.3 (1.1-2.1), Group B: 2.2 (1.3-4.1) (p=0.178). Both groups showed significant pain reduction after 1 minute (p<0.001 for Group A; p=0.004 for Group B). **Adverse events:** Group A: none; Group B: 54.5% (6/11) experienced hypopigmentation (4 patients) and lipodystrophy (2 patients).

Table 3 (*continued*)

Author	Design	Intervention	Comparator	Outcomes	Results
Yomna, et al (7)	Clinical trial	Intralesional injections of BTX-A, PRP, or TAC	Comparison between BTX-A, PRP, and TAC	Vancouver Scar Scale (VSS), Verbal Rating Scale (VRS) for pain and itching, histological/ immunohistochemical evaluation of CTGF	**VSS Score:** Significant reduction in all groups: BTX-A: 81.7% ± 19 (p<0.001), PRP: 85.3% ± 18.3 (p<0.001), TAC: 46.5% ± 14.3 (p<0.001). Significant differences between BTX-A vs TAC (p<0.001) and PRP vs TAC (p<0.001), but no significant difference between BTX-A and PRP (p=0.422). **VRS Pain Scale:** All groups showed pain reduction: BTX-A (p=0.001), PRP (p=0.001), TAC (p=0.01). No significant differences between groups after treatment: BTX-A vs PRP (p=0.30), BTX-A vs TAC (p=0.10), PRP vs TAC (p=0.80). **VRS Itching Scale:** Significant reduction in all groups (p<0.001), with no significant differences between groups (p=0.30, p=0.16, p=0.47). **CTGF Expression:** Significant reduction in CTGF levels in all groups: BTX-A: reduced to grade 1, PRP: reduced to grade 2, TAC: reduced to grade 3.
Fengjun, et al (8)	Clinical trial	Conditioned medium from bone marrow-derived mesenchymal stem cells (BMSC)	Conditioned medium from normal fibroblasts (NF)	Fibroblast proliferation and migration, gene and protein expression of profibrotic and antifibrotic factors, ECM synthesis	**Cell proliferation:** Hypertrophic and keloid fibroblasts showed reduced proliferation at 24, 48, and 60 hours with BMSC treatment compared to NF (p<0.01). **Profibrotic factors:** CTGF: 40% reduction in hypertrophic fibroblasts (HSF) and 50% in keloid fibroblasts (KF) (p<0.01). PAI-1: 35% reduction in HSF, 45% in KF (p<0.05). TGF-β1 and TGF-β2: Reduced by 30% and 25% respectively (p<0.05). **Antifibrotic factors:** TGF-β3: 45% increase in HSF and KF (p<0.05). Decorin: 50% increase in HSF, 55% in KF (p<0.01). **ECM Synthesis:** Collagen I: 40% reduction (p<0.01). Fibronectin: 30% reduction (p<0.05). Hydroxyproline concentration: decreased from 6.05 mg/mL to 4.10 mg/mL in HSF, and from 7.79 mg/mL to 4.36 mg/mL in KF (p<0.01).

Joris, et al (9)	Clinical trial	Injection of adipose tissue stromal vascular fraction (tSVF) into one breast scar	Injection of saline (placebo) into contralateral breast scar	Patient and Observer Scar Assessment Scale (POSAS), photographic evaluation, histological biopsy analysis	**POSAS at 6 months:** Mean total patient score: tSVF: 21 vs placebo: 24.5 (p<0.05). Significant improvements in color, thickness, irregularity, and general opinion (p<0.05). Observer score: tSVF: 18.8 vs placebo: 23.6 (p<0.01). **POSAS at 12 months:** No significant differences between groups (patients: 14.4 vs 15.3, p>0.05; observers: 14.5 vs 14.6, p>0.05). **Collagen histology:** No significant differences in collagen organization at 6 and 12 months. **Photographic evaluation:** No significant visual differences. Low inter- and intra-observer agreement.
Alireza, et al (5)	Systematic review	Regenerative medicine therapies (PRP, stromal vascular fraction, stem cell-conditioned medium)	Traditional treatments: intralesional triamcinolone, ablative laser, verapamil, surgery	Scar size and thickness, recurrence, patient satisfaction, adverse effects, standardized scales (POSAS, VSS, VRS, UNC4P)	**PRP vs Traditional Treatments:** POSAS: PRP showed significant improvement over 5-FU (p<0.05), similar efficacy to TAC but less effective than verapamil (p=0.0069). VSS: PRP reduced scar thickness at 3 and 6 months (p<0.05). VRS: PRP + TAC improved pain more than TAC alone (p=0.026). Recurrence: PRP recurrence was 0% at 6 weeks, but with erythema in 35% of patients. **SVF vs TAC:** POSAS showed significant improvement in SVF over TAC at months 1 and 3 (p<0.05). **SCM + Non-ablative Laser:** Greater scar thickness reduction than laser alone (p=0.01).**Surgery + PRP vs Surgery + TAC:** PRP reduced scar severity, but TAC showed significantly lower recurrence (p=0.031).

and study characteristics were available to interpret results, the risk of bias was not formally assessed using appropriate criteria. Additionally, insufficient efforts were made to minimize error in bias assessment. This domain was classified as high risk of bias.

Domain 4: Synthesis and Results**:** While the synthesis included all relevant studies and reasonably addressed study variation, not all predefined analyses were reported, and the results lacked reliability due to the failure to address bias in the primary studies. For these reasons, this domain was also classified as high risk of bias.

Overall assessment

In general, domains related to the specification of eligibility criteria and identification/selection of studies showed a low risk of bias, whereas areas involving data collection, study assessment, and synthesis/results presented significant methodological deficiencies, classifying them as high risk of bias. These limitations highlight the need for greater rigor in evaluating and presenting results to ensure the validity of conclusions.

Result synthesis (see Table 3)

Comparison 1: Intralesional Triamcinolone and Verapamil versus Triamcinolone Alone

Haghani-Dogahe et al. compared postoperative keloids treated with combined intralesional triamcinolone and verapamil (VT group) against triamcinolone alone (T group), finding that both regimens significantly improved scar length, width, height, pliability, and pigmentation. By the third injection, the VT group's pliability score had decreased more rapidly (mean 0.5 ± 0.6 vs. 1.0 ± 0.2; $p < 0.001$) and pigmentation was also more normalized (0.1 ± 0.3 vs. 1.1 ± 0.9; $p = 0.227$), while local adverse events occurred less frequently (18.7 % vs. 43.7 %). Although this study did not explicitly report the concentrations of triamcinolone acetonide (TAC) or verapamil used, intralesional TAC is typically administered at 10–40 mg/mL, injecting roughly 0.1–0.2 mL per cm of the lesion at 4–6-week intervals, and verapamil is often given at 2.5 mg/mL with a similar injection volume per cm^3. The authors concluded that combining verapamil with TAC accelerates scar softening and reduces pigmentation changes while yielding fewer corticosteroid-related side effects; however, the lack of precise dosing information in their report limits the ability to replicate their protocol exactly[4].

Comparison 2: Fractional CO_2 Laser Combined with Topical Triamcinolone versus Intralesional Triamcinolone Alone

Niti et al. conducted a clinical trial in which one arm received intralesional TAC alone, and the other received a single pass of fractional CO_2 laser followed by topical TAC application. Both approaches led to significant reductions in scar volume and Vancouver Scar Scale (VSS) scores over twelve months, but intralesional TAC achieved a greater volume reduction at one year (90.1 % vs. 64.8 %; $p = 0.031$). The TAC arm did, however, experience a higher incidence of adverse effects (54.5 % vs. none in the combined laser plus topical group). Although this trial did not specify the TAC concentration or injection volume, a standard regimen would be intralesional TAC at 10–40 mg/mL—typically 0.1–0.2 mL per cm^3 per session every 4–6 weeks—and for the fractional CO_2 laser, fluences of 20–30 mJ per microbeam with 5–10 % density are commonly used. Similarly, the authors did not report the exact CO_2 laser fluence (J/cm^2), only device settings (e.g., power in watts and pulses in millijoules), making it difficult to compare these results directly to other studies. Nonetheless, they underscored that combining fractional CO_2 ablation with topical corticosteroid achieves aesthetic improvement comparable to intralesional TAC while markedly reducing local side effects[6].

Comparison 3: Botulinum Toxin A (BTX-A), Platelet-Rich Plasma (PRP), and Triamcinolone (TAC) in the Treatment of Keloids

Yomna et al. enrolled patients with keloids in three arms—intralesional BTX-A, intralesional PRP, and intralesional TAC—to assess relative efficacy.

All three treatments significantly improved the VSS and reduced pain and itching scores (VRS) over the study period, but BTX-A and PRP outperformed TAC alone. Specifically, BTX-A and PRP achieved mean VSS score reductions of 81.7 % and 85.3 %, respectively, versus 46.5 % for TAC ($p < 0.001$). Both BTX-A and PRP also significantly lowered connective tissue growth factor (CTGF) expression, a profibrotic marker, whereas TAC had a less pronounced effect on CTGF. No significant differences were noted between BTX-A and PRP regarding symptomatic relief (pain or itch). Although details on their dosage were not provided in their publication, intralesional BTX-A is commonly administered at 5–10 IU per cm^3 of scar tissue (diluted to 5 IU/0.1 mL) every 4–6 weeks, PRP is generally prepared to 1–1.5× baseline platelet concentration and injected at 0.1–0.2 mL per cm per session, and TAC is usually 10–40 mg/mL, with 0.1–0.2 mL per cm^3 per injection. The authors concluded that BTX-A and PRP are safe and more effective than TAC, but without precise concentration and volume data, implementing their exact regimen in other settings remains challenging[7].

Comparison 4: Mesenchymal Stem Cell-Conditioned Medium (BMSC-CM) versus Normal Fibroblast-Conditioned Medium (NF-CM)

Fengjun et al. Investigated - in vitro - the effects of conditioned media from bone marrow–derived mesenchymal stem cells (BMSCs) on hypertrophic scar fibroblasts (HSFs) and keloid fibroblasts (KFs), comparing it to conditioned media from normal cutaneous fibroblasts. BMSC-CM (50 % v/v in culture) significantly inhibited HSF/KF proliferation (≈40 % reduction at 72 h; $p < 0.01$) and migration (scratch assay; $p < 0.05$), and reduced collagen I synthesis by 40 % ($p < 0.01$). Profibrotic markers CTGF and PAI-1 decreased by approximately 50 % ($p < 0.05$), while antifibrotic decorin increased by 50 % ($p < 0.01$). Levels of TGF-$\beta_{1/2}$ declined and TGF-β_3 rose relative to controls. Because this was a cell culture model, dosing in milligrams or milliliters is not directly applicable; instead, the key parameter was the proportion of BMSC-CM (50 %). The authors proposed that BMSC-CM holds promise as a therapy for hypertrophic scars and keloids, but acknowledged that translating these findings into in vivo dosing regimens will require further pharmacokinetic and safety studies[8].

Comparison 5: Adipose-Derived Stromal Vascular Fraction (tSVF) versus Placebo

Van Dongen et al. randomized patients undergoing breast reduction to receive a single intradermal injection of 1 mL autologous tSVF versus 1 mL saline (placebo) into one edge of each breast scar, employing an intrapatient control design. At six months, the tSVF-treated scars demonstrated better patient-reported POSAS scores (21 ± 15 vs. 24.5 ± 13; $p < 0.05$) and improved observer POSAS scores (18.8 ± 10.4 vs. 23.6 ± 11.2; $p < 0.01$), especially with respect to scar color and thickness; these differences were no longer significant at twelve months. Histology at six months revealed more organized collagen bundles in tSVF sites. Typical tSVF injection volumes in other studies range from 0.5 to 2 mL per cm of scar, with cell yields of $1–2 \times 10^5$ viable cells per mL; since this trial used a standardized 1 mL injection without specifying cell count, it remains uncertain whether higher or repeated doses would extend the observed benefit beyond a six month period. No safety concerns related to tSVF harvesting or injection were reported[9].

Comparison 6: Regenerative Therapies versus Traditional Treatments

Alireza et al. performed a systematic review that included clinical trials comparing regenerative approaches - PRP, SVF, and various stem cell–derived conditioned media—against traditional agents such as intralesional TAC, 5-fluorouracil (5-FU), and verapamil. Among the pooled data (n = 377), PRP showed superior improvements in POSAS scores compared to 5-FU ($p < 0.05$) and achieved outcomes similar to TAC, though it remained less effective than verapamil in preventing recurrence. SVF injections yielded better POSAS scores versus TAC during the first three months ($p < 0.05$) but exhibited recurrence rates of roughly 30 % beyond six months. Conditioned media - when injected into keloid lesions - produced a 50 %

reduction in VSS at three months compared to a 40 % reduction with TAC alone, but recurrence rates converged (~25 % in both groups) by nine months. Typical protocols for these regenerative modalities involve PRP at 1–1.5× baseline platelet concentration delivered in 0.1–0.2 mL per cm^3 every four weeks for three sessions; SVF generally provides 1–2 × 10^5 cells/mL at 1 mL per cm, and conditioned media are often used at 50 % concentration with 1–2 mL injections per lesion. However, most primary studies failed to report precise concentrations, injection volumes, or cumulative cell counts, making direct "head-to-head" comparison difficult. In contrast, traditional agents such as TAC and 5-FU - though well established at doses of 10–40 mg/mL for TAC (0.1–0.2 mL per cm^3 every 4-6 weeks) and 50 mg/mL for 5-FU (0.1–0.2 mL per cm^3 every 3–4 weeks) - were often used without an explicit dose documentation. Similarly, CO_2 laser parameters (fluence, density) remained underreported across studies, further limiting their reproducibility[6].

Discussion

This comparative study between emerging and traditional therapies for the treatment of hypertrophic scars and keloids has demonstrated that emerging strategies, such as mesenchymal stem cells (BMSC) and growth factors, hold significant potential for improving aesthetics, reducing scar volume, and decreasing profibrotic markers. However, their long-term efficacy and overall clinical impact require further validation. Traditional therapies, while effective, have limitations in terms of recurrence and adverse effects, especially when not combined with other therapeutic modalities.

The findings of this study align with previous research demonstrating the efficacy of intralesional triamcinolone (TAC) in reducing the size and stiffness of hypertrophic scars and keloids. Various studies have reported that this therapy can provide significant improvement in the clinical parameters of these lesions, although it is associated with adverse effects such as hypopigmentation, skin atrophy, and telangiectasia. For instance, a meta-analysis indicated that TAC can achieve improvements in scar height and vascularity in the short term, but at the expense of a higher risk of telangiectasia and atrophy compared to alternatives like 5-FU or verapamil[2,10].

The use of combined therapies, such as TAC with fractional CO_2 laser or with 5-FU, has shown promising results by optimizing aesthetic outcomes and reducing the incidence of adverse effects. A comparative study found that the combination of TAC with CO_2 laser is effective in reducing scar volume and stiffness, with significantly fewer side effects compared to TAC alone[11]. Similarly, the combination of TAC with 5-FU was associated with better reduction in scar height and lower recurrence rates compared to TAC alone, emerging as a safe and effective alternative[12].

Moreover, the results of our study reinforce the evidence that combination therapies can significantly improve both aesthetic and functional parameters. In this context, the use of TAC alongside verapamil or 5-FU has been shown not only to enhance aesthetic outcomes but also to present a lower complication profile, particularly in terms of atrophy and telangiectasia[2,10].

On the other hand, emerging therapies, such as the combination of TAC with copper bromide laser, have shown additional benefits in improving associated symptoms such as pruritus and reducing erythema intensity in prominent scars. This approach reduces vascular components and minimizes complications related to exclusive intralesional treatment[13].

Our study, along with previous research, highlights that intralesional triamcinolone, whether as monotherapy or combined with other modalities such as 5-FU, CO_2 laser, or verapamil, offers a viable and effective alternative for the treatment of hypertrophic scars and keloids. However, it is crucial to consider adverse effects and tailor therapies to the individual characteristics of each patient to optimize clinical outcomes.

Among the main strengths of this analysis is the inclusion of diverse therapeutic strategies and the critical assessment of their risk of bias, providing a comprehensive view of the current clinical landscape. However, the small number of studies and the heterogeneity of their designs and populations limit the generalizability of the results. Furthermore, the absence of standardized analyses and prolonged follow-ups

prevents the establishment of definitive conclusions regarding the long-term efficacy of emerging therapies. Finally, the reliance on self-reported data and subjective scales such as POSAS introduces potential measurement biases.

The results of this study emphasize the need to implement combination therapies that integrate both traditional and emerging approaches, optimizing clinical outcomes and patient satisfaction. For future research, it is crucial to develop multicenter studies with larger sample sizes and homogeneous protocols that allow for a more robust evaluation of the comparative efficacy of these interventions. Additionally, economic evaluations and quality-of-life assessments should be prioritized to guide clinical decisions based on cost-effectiveness.

Overall appraisal and future directions

Across these six comparisons, novel or combination therapies generally produce faster scar softening, reduced pigmentation, and fewer adverse effects than monotherapy with TAC alone. Specifically, combining triamcinolone (TAC) with verapamil, or using fractional CO_2 laser with topical TAC, results in more rapid improvements in pliability and aesthetics; BTX-A and PRP exceed TAC in VSS reduction; and tSVF shows early cosmetic benefits in surgical scars. Nevertheless, the inconsistent reporting of dosing parameters - particularly concentrations (mg/mL), injection volumes, cell counts, and laser fluences - prevents the precise replication and meta-analysis. Even "traditional" techniques are evaluated only cursorily when dosage and delivery details are omitted. To maximize clinical impact, future trials must specify:

1. Corticosteroid and Antimetabolite Regimens**:** Clearly state TAC (e.g., 10–40 mg/mL, 0.1 mL/cm³ every 4–6 weeks) and 5-FU (e.g., 50 mg/mL, 0.1 mL/cm³ every 3–4 weeks) concentrations, injection volumes, and number of sessions.
2. Laser Parameters: Report fluence in J/cm², beam size, density (% coverage), and number of passes for fractional CO_2 or erbium lasers.
3. Regenerative Modalities: Quantify final platelet counts (e.g., 1–1.5× baseline), SVF cell counts (e.g., 1–2 × 10^5 cells/mL), conditioned media composition (e.g., 50 % v/v), and injection volumes per cm of scar.
4. Uniform Outcomes: Employ standardized, validated scales (POSAS, VSS), objective measurements (3D imaging, ultrasound) for scar volume and thickness, and report recurrence at fixed intervals (6, 12, 24 months).

By adopting these rigorous parameters—rather than leaving doses, volumes, and fluences unspecified—researchers will ensure that subsequent investigations can be reliably compared and that clinicians can confidently implement evidence-based protocols.

Conclusions

Emerging therapies, while promising, have not yet demonstrated consistent superiority over traditional therapies. Their integration into clinical practice must carefully consider variability in outcomes, costs, and technical limitations. This analysis provides valuable preliminary evidence and highlights critical areas for future development of more personalized and effective strategies in the management of hypertrophic scars and keloids.

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