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REVIEW ARTICLE

Management of hypertrophic scars in adults: A systematic review and meta-analysis

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ABSTRACT

Hypertrophic scars (HTS) are elevated scars which occur due to abnormalities in wound healing after injury and may be associated with pain, pruritus and functional impairment. Despite multiple available treatment options, there is no universal approach to treating HTS. We searched the Web of Science (Core Collection), MEDLINE and EMBASE databases. Title, abstract and full-text screening, along with data extraction, were performed in duplicate. Risk of bias was assessed using the Cochrane risk-of-bias tool. The Vancouver Scar Scale (VSS) scores and mean differences were used for meta-analysis. We screened 3800 abstracts and included 34 randomised controlled trials evaluating treatments for HTS in adults. Silicone and laser modalities improved VSS scores by 5.06 (95% CI: 6.78, 3.34) and 3.56 (95% CI: 5.58, 1.54), respectively. Intralesional triamcinolone combined with silicone or 5-fluorouracil was superior to intralesional triamcinolone monotherapy. Limitations of this study include exclusion of studies which did not utilise VSS, and pooling of studies based on common modalities. Further studies are needed to examine the efficacy of existing and emerging treatment modalities for HTS. Our study supports the treatment of HTS in adults with silicone gel or sheets, injected triamcinolone (preferably combined with 5-fluorouracil or silicone products), pulsed dye laser and fractionated CO_2 laser.

Key words: hypertrophic scar, management, review, treatment, wound healing.

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Abbreviations:

5-FU	5-fluorouracil
AE	adverse event
BTX-A	botulinum toxin type A
CO_2	carbon dioxide
ECM	extracellular matrix
Er:YAG	erbium yttrium aluminium garnet
FCO_2	fractional CO_2
GAS	global assessment score
HTS	hypertrophic scars
IPL	intense pulsed light
ITT	intention-to-treat
MD	mean differences
MSS	Manchester Scar Scale
NAFR	non-ablative fractional resurfacing
Nd:YAG	neodymium-doped yttrium aluminium garnet
PDL	pulsed dye laser
PGA	patient global assessment
PhGA	physician global assessment
POSAS	Patient and Observer Scar Scale
RCT	randomised controlled trial
ROB	risk of bias
SD	standard deviation
TAC	triamcinolone acetonide
VAS	visual analog scale
VSS	Vancouver Scar Scale

WHAT THIS RESEARCH ADDS

- What this research adds is a rigorous up to date review of the management of a common and important problem.

INTRODUCTION

Hypertrophic scars (HTS) are visible, elevated scars caused by abnormal wound-healing processes secondary to dermal injury[1] and may result in pain, pruritus, reduced aesthetics and functional impairment.[2–4] HTS occur when there is either an insufficient degradation or remodelling of extracellular matrix (ECM) proteins due to imbalances in the expression of matrix metalloproteinases, or due to excessive ECM deposition from hyperactivity of fibroblasts and myofibroblasts.[1] Although HTS may form after any mechanism of skin injury, they are estimated to occur in 40–70% of surgical patients, in up to 90% of burn patients[2] and in 14% of patients with acne.[5]

Current guidelines recommend silicone sheets or gel as a first-line agent for preventing and treating HTS.[6,7] Silicone promotes hydration and subsequently decreases capillary activity and collagen deposition but can cause contact dermatitis.[6,7] Other studies support the use of intralesional injection of triamcinolone acetonide (TAC), which decreases inflammation while increasing vasodilation,[8] but is associated with increased risk for hypopigmentation, skin atrophy and telangiectases.[7] Several reports utilised novel treatment modalities, including lasers, and pressure garments.[9] Despite the numerous treatment options available, there is no universally accepted approach to managing HTS. The aim of this systematic review was to determine the most effective treatment options for HTS in adults.

METHODS

We conducted a systematic review of the literature adhering to PRISMA reporting guidelines.[10] Our protocol was registered and published on the PROSPERO database (CRD42020173635).

Study eligibility criteria

Eligibility criteria for this review were as follows:

- Population: adults (age > 18) with HTS.
- Intervention: any HTS treatment modality, regardless of previous treatments received, duration of therapy or length of follow-up.
- Comparator: non-intervention or criterion standard (intralesional TAC).
- Outcomes: quantitative and qualitative assessments of scars including symptomatic improvements.
- Study design: randomised control trials (RCT).Studies examining patients with keloids in addition to HTS were only included if subgroup data were available, and only the data from patients with HTS were included in the analysis.

Exclusion criteria

Non-human studies, non-English studies and non-original studies were excluded from this review. Studies including patients with HTS and keloids that did not perform a subgroup analysis were excluded. Studies exclusively examining keloid scars were excluded.

Primary and secondary outcomes

Primary outcomes were improvements to HTS characteristics, including the following: mean scar size, pigmentation, pliability and symptomatic improvement. These characteristics were reported by participants or observers using various standardised scoring scales [e.g. Vancouver Scar Scale (VSS)] (Table S1). Secondary outcomes were adverse reactions to interventions.

Risk of bias

Studies included in full-data extraction were independently assessed by five reviewers (A.J., C.C., R.R., M.S. and M.S.) using the Cochrane risk-of-bias tool (version 2.0).[11] This tool utilises the following domains to assess bias: randomisation process, deviations from intended interventions, missing outcomes, measurement of outcome and selection of the reported result. The overall risk of bias for each study was generated by the algorithm included in the Cochrane risk-of-bias tool.[11] The risk of bias was judged to be in one of three categories: low, some concerns and high. Conflicts were resolved by discussion until a consensus was reached with input from the senior reviewer (I.M.).

Literature search and screening

We searched MEDLINE and EMBASE from 1980 to 31 December 2019 using the OVID interface. We additionally searched the Web of Science database and hand-searched reference lists of included studies. Search keywords and MeSH terms used are listed in Tables S2–S4.

The search strategy was developed in collaboration with a biomedical librarian and a statistician (V.K. and C.L). Title, abstract and full-text screening were conducted independently in duplicate by five reviewers (A.J., C.C., M.S., M.S. and R.R.) using Covidence software.[12] Full-text screening was performed on studies to be included. At the full-text screening stage, studies were excluded if they did not follow the predetermined PICOS criteria. Disagreements were resolved through discussion and with input from the senior reviewer (I.M.) when necessary.

Data extraction

Data extraction was completed by two of the five reviewers (A.J., C.C., R.R., M.S. and M.S.) on a standardised extraction form. Extracted data included the following: title, authors, year of publication, gender and age of participants, number of patients, scar aetiology, Fitzpatrick skin types, treatment modality, follow-up period, outcome measures used and values for the outcomes before and after treatment. If data items were incomplete, additional information was obtained by contacting the authors.

Meta-analysis

Mean VSS scores with standard deviations (SD) before and after treatment were extracted from primary studies. VSS was chosen as the standard because it was the most commonly used outcome measure in the studies included in our meta-analysis. Studies which did not report one or both of those values were excluded from analysis. Mean differences before and after each treatment were computed. Random-effects models for mean differences were fitted for the entire pool of studies, and for subgroups of studies using a specific modality, such as laser, silicone, intralesional TAC, other treatments (microneedling, onion extract gel, pressure garments) and no treatment, and a test for subgroup differences was computed. All analyses were completed in R using the metafor statistical package.

RESULTS

Our literature search yielded 6313 non-duplicate articles, 6156 were excluded from title and abstract review (Fig. 1). Of the 157 studies retrieved for full-text screening, 123 were excluded. Thirty-four studies were included in this review, and seven studies met the criteria to be included in the meta-analysis.

Study characteristics

The 34 included studies were published between 1992 and 2019 (Table 1). Studies were conducted in Canada ($n = 1$), the United States of America ($n = 5$), Egypt ($n = 4$), Iran ($n = 7$), China ($n = 4$), South Korea ($n = 3$), Germany ($n = 2$), Pakistan ($n = 2$), Belgium ($n = 1$), Brazil ($n = 1$), Hungary ($n = 1$), Turkey ($n = 1$), the Netherlands ($n = 1$) and the United Kingdom ($n = 1$). In total, 1410 patients were included in our analysis. Mean age was 33 years (range 3–81). Of the 1410 patients, 662 were male, 615 were female, and 133 were of unspecified gender. Mean follow-up was 4 months (range 1–18).

Lasers

Pulsed dye laser (PDL) was examined in five studies (Table 2). PDL was superior to both TAC and erbium yttrium aluminium garnet (Er:YAG) laser in lowering VSS (54% reduction for PDL, $P < 0.01$ *vs* 25% for TAC, $P > 0.043$ *vs* 49% for Er:YAG, $P < 0.024$),[13] but showed no statistically significant difference when compared to fractional carbon dioxide (FCO_2) laser[14] or to long-pulsed neodymium-doped yttrium aluminium garnet (Nd:YAG) laser alone.[15] PDL combined with FCO_2 laser was superior to PDL (66% *vs* 57% improvement in VSS, $P < 0.05$)[16] or FCO_2 laser alone (35% *vs* 56% improvement in global assessment score (GAS), $P = 0.003$).[17] However, in a split-scar study of 20 patients, Wittenberg and colleagues [18] demonstrated that neither PDL nor silicone gel sheets showed differences in improvement in blood flow, elasticity, volume, pruritus, pain and burning in HTS compared with the control group.

FCO_2 was evaluated in seven studies. FCO_2 laser led to a greater decrease in VSS compared with placebo (43% *vs* 0%, $P = 0.027$)[19] and Er:YAG laser (51% *vs* 27%).[20] Intense pulsed light (IPL) and FCO_2 laser combined showed greater improvement in the Manchester Scar Scale (MSS) and POSAS compared with FCO_2 laser alone (40% *vs* 36% decrease in MSS, $P < 0.001$ and 70% *vs* 36% decrease in POSAS, $P < 0.001$).[21]

Er:YAG laser was evaluated in two studies and showed limited efficacy. FCO_2 laser was shown to be superior to Er:YAG laser in reducing VSS.[20] Both thermal and thermoablative mode settings of Er:YAG laser were shown to be effective in reducing redness, hardness and scar elevation (73% and 53% reduction in total score from baseline, $P < 0.001$), and the addition of silicone gel did not produce any additional benefit (42% *vs* 41% reduction in total score from baseline, $P < 0.001$).[22]

Non-ablative fractional resurfacing (NAFR) was evaluated in two studies. In a split-scar study of 22 patients, NAFR reduced pain although the magnitude of the improvement was not reported in this study.[23] NAFR did not produce a significant improvement on the VAS measured by blinded physician observers.[23] Another split-scar study showed NAFR was effective in improving overall appearance as assessed by patients (48%, $P = 0.03$ and 75%, $P = 0.001$ improvement for high-density and low-density NAFR respectively).[24] However, pigmentation, erythema, texture and overall appearance as assessed by both blinded observers and patients did not reach statistical significance when compared to control.

Injections

Intralesional TAC was evaluated in six studies. As discussed above, PDL and TAC combined showed greater reduction of VSS compared with TAC monotherapy.[13] TAC and silicone sheeting in combination were superior to TAC alone in reducing VSS scores although the magnitude of improvement was not specified.[25] Combination therapy of TAC and 5-FU was noted to be superior in decreasing scar height (69% *vs* 47%, $t = 4.781$, $P < 0.001$) and preventing recurrence (18% *vs* 39%, $P = 0.012$) *vs* TAC alone.[26] Studies comparing TAC to silicone monotherapy reported mixed results. In a half-scar study, silicone gel had a shorter time to improvement (3.9 days *vs* 6.8 days, $P < 0.05$) and was more favoured by patients (2 of 14 patients favoured TAC, 11 of 14 patients favoured silicone, and 1 patient had no preference) compared with TAC.[27] Furthermore, silicone led to greater improvement in VSS

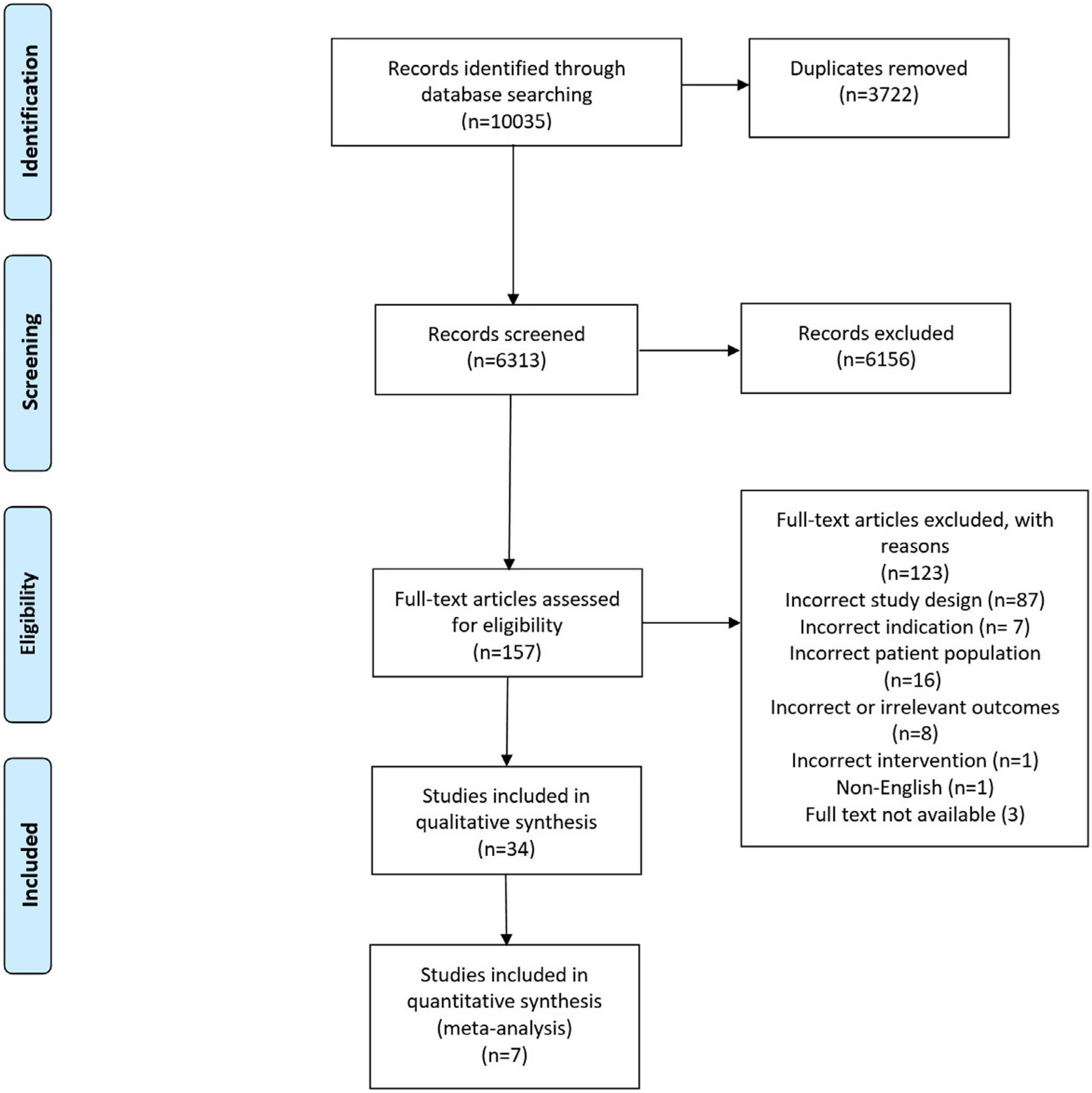

Figure 1 PRISMA diagram of study selection process.

compared with TAC (62% *vs* 25%, $P = 0.0001$).[28] However, another study found TAC and silicone gel sheeting resulted in comparable improvements in VSS scores.[29]

Botulinum toxin type A (BTX-A), pentoxifylline and EXC001 (an antisense oligonucleotide targeting skin tissue growth factor) were evaluated in one study each. Compared to placebo, BTX-A showed a statistically insignificant ($P > 0.09$) 20% decrease in scar pliability, vascularity, pigmentation and height.[30] Pentoxifylline was associated with limited efficacy, although the findings may only apply to patients with peribuccal HTS. Pentoxifylline increased the degree of mouth opening, a surrogate measurement for scar elasticity, by approximately 8% compared with placebo ($P < 0.001$).[31] In a study examining equal bilateral scars after breast surgery, the scar treated with EXC001 combined with surgery was associated with lower physician-rated POSAS (3.6 *vs* 6.0), patient-rated POSAS (4.1 *vs* 6.5) and VAS scores (30.7 *vs* 56.7) compared to the scar treated with surgery alone.[32]

Table 1 Characteristics of included studies

Author, year	($n^{\dagger}$)	Mean age (years)	Ethnicity (study site[‡])	Scar aetiology	Scar duration	Lost to F/U	Treatment arms	Outcomes used	Key findings	Risk of bias
Al-Mohamady, 2016	11	22.6	(Egypt)	Burn, surgical, trauma	N/A	0	PD, Nd:YAG	VSS	Both treatments provided significant improvement to keloids and HTS	High
Ali, 2016	29	31.71	(Pakistan)	Burn	N/A	0	TAC, TAC + 5-FU	Efficacy (50% reduction in scar size)	TAC and 5-FU were superior to TAC alone	High
Alshehari, 2015	30	A: 24 B: 26	(Egypt)	Burn, surgical, trauma	N/A	0	A: TAC, B: TAC + silicone	VSS	TAC and silicone were superior to TAC alone in improving mean pigmentation, thickness score and mean thickness	High
Alster, 1998	20	37 (16–55)	(USA)	NR	2.5 years	0	FCO_2, FCO_2 + PDL	GAS, erythema	Combination FCO_2 and PDL laser treatment were superior to FCO_2 laser alone	High
Azzam, 2015	12	24.5 ± 9.4	(Egypt)	NR	N/A	5	FCO_2 (split-scar study)	VSS, patient satisfaction	FCO_2 resulted in significant improvements in VSS	High
Cho, 2014	160	A: 47.2 ± 8.2 Ctl: 46.1 ± 8.6	(Korea)	Burn, skin graft	N/A	14	A: Burn rehabilitation massage	Pain, pruritus	Burn rehabilitation massage therapy is effective in improving pain, pruritus and scar characteristics in hypertrophic scars after burn	Med
Choi, 2014	23	A: 32.8 B: 37.2	Korean	NR	6.4 years	NR	A: Er:YAG laser, B: FCO_2	VSS	FCO_2 was superior to Er:YAG fractional laser	High
Daoud, 2019	23	N/A	(USA)	NR	>1 year	4	FCO_2, IPL + FCO_2	POSAS, MSS	Combination treatment was superior to FCO_2 laser alone, although the difference in overall MSS was not statistically significant	High
Harte, 2009	30	36.8 ± 14.7	(Northern Ireland)	Burn	≤6 months	4	Pressure garments, pressure garments + silicone	Modified VSS	No significant difference in modified VSS reduction between pressure therapy + silicone *vs* pressure therapy alone	High
Hedayatyanfard, 2018	37	A: 31.7 ± 15.5 Ctl: 47.6 ± 27.6	(Iran)	Acne, burn, scald, surgical	≥6 months	7	A: Losartan ointment	VSS	Losartan ointment reduces VSS compared to placebo in hypertrophic scars, with no return of scars observed 6 months following therapy cessation	High
Isaac, 2010	18	12–45	(Brazil)	Burn	≥6 months	0	Pentoxifylline	Scar elasticity *via*: maximum oral opening and dental distance	Pentoxifylline increased perioral hypertrophic scar elasticity compared with placebo	High

Table 1 *Continued*

Author, year	($n^{\dagger}$)	Mean age (years)	Ethnicity (study site[‡])	Scar aetiology	Scar duration	Lost to F/U	Treatment arms	Outcomes used	Key findings	Risk of bias
Jensen, 2018	25	42.5 ± 9.07	(USA)	Surgical	6 months-6 years	4	EXC001	POSAS, expert rated scale (0–100)	EXC 001 produced a significant reduction in severity of postsurgical skin scars	Low
Karagoz, 2009	32/45	24 (3–55)	(Turkey)	Burn (non-chemical)	<6 months	0	Silicone gel, silicone gel sheet, topical onion extract	VSS	All three treatment modalities (silicone gel, silicone gel sheet, onion gel extract) resulted in significant improvements to VSS scores, but silicone products (gel or sheet) were superior to onion gel extract	High
Kelemen, 2008	24	N/A	(Hungary)	NR	N/A	0	Silicone gel sheet, TAC	VSS	Both intralesional steroid and silicone gel resulted in similar improvement in VSS score, with intralesional steroids acting more rapidly in their onset	High
Khalid, 2019	120	A: 31.2 ± 12.5 B: 27.7 ± 9.5	(Pakistan)	Burn, piercing, trauma	N/A	12	A: TAC, B: TAC + 5-FU	Mean scar height, efficacy	TAC + 5-FU resulted in greater decreases in scar height and lower recurrence rate when compared to TAC alone	High
Lai, 2010	17/53	26.23 ± 7.78	Chinese	Burn, scald, surgical, trauma	N/A	0	Low-pressure garment, high-pressure garment	Interface pressure (mmHg), thickness, colour (VSS), pliability (VSS)	High-pressure therapy was better in reducing thickness and redness compared with low-pressure therapy, but resulted in greater degradation of interface pressure over time	High
Li-Tsang, 2006	45	29.65 ± 17.60	Chinese	Burns (thermal, electrical, chemical), scalds, trauma	N/A	3	Silicone gel sheeting, Ctl: Lanolin deep massage	Thickness (VSS), pliability (VSS)	Silicone gel sheeting resulted in significant reduction of thickness, improvements in softness, pliability, pain, itchiness compared with control	Low
Li-Tsang, 2010	104	21.8 ± 18.7	Chinese	Burn, (chemical and thermal), scald, trauma	N/A	20	Pressure therapy, silicone gel sheeting, pressure therapy + silicone gel sheeting, Ctl: Lanolin deep massage	Colour, thickness, pliability (VSS), pain (VAS), itchiness (VAS)	Combined therapy with silicone gel dressing and pressure therapy resulted in greatest improvements in thickness, whereas silicone gel alone was more effective in alleviating pain and pruritus	High

Table 1 *Continued*

Author, year	($n^†$)	Mean age (years)	Ethnicity (study site[‡])	Scar aetiology	Scar duration	Lost to F/U	Treatment arms	Outcomes used	Key findings	Risk of bias
Lin, 2011	20	39	(USA)	Surgical	≥6 months	3	NAFR HDTA, NAFR LDTA	Physician rating scale, patient rating scale, volume reduction	LDTA is as effective as HDTA with fewer side effects	High
Mehran, 2019	60	A: 32 B: 37	(Iran)	Burn	N/A	0	A: Microneedling, B: FCO_2	VSS, VAS	Microneedling had better outcomes than FCO_2 at 3 months	Low
Mohamma-di, 2018	30	N/A	(Iran)	Burn	N/A	0	Enalapril	Scar size, daily itch score	Enalapril-treated scars were smaller in size compared with placebo and had lower itching scores	Low
Momeni, 2009	34	22 (1.5–60)	(Iran)	Burn	2–4 months	4	Silicone gel sheet	VSS	All scores except pain were significantly lower in the silicone gel group compared with the control group	Low
Omranifard, 2007	120	27.2 ± 4.8	Iranian	Surgical, trauma	<1 year	NR	TAC, PDL, Er:YAG	VSS	PDL was more effective at lowering VSS compared with TAC and Er:YAG	Low
Ouyang, 2018	56	3–51	(China)	Burns, scalds, surgical, trauma	<3 months	0	PDL, PDL + FCO_2	VSS	Combination therapy was superior to PDL alone	Low
Radmanesh, 2019	35	23.23 (4–34)	(Iran)	Burn, surgical, trauma	2 years	0	PDL, FCO_2 (split-scar study)	VSS	No statistical differences in performance between PDL and FCO_2	Low
Song, 2018	90	A: 38.0 ± 6.5, B: 39.1 ± 6.0, Ctl: 38.5 ± 6.7	Asian	Surgical	N/A	3	A: Silicone gel, B: onion extract gel	VSS	Silicone gel and onion extract gel had similar compliance, side effects and efficacy	Low
Sproat, 1992	14	41–81	(Canada)	Surgical	4 months–1 year	0	TAC, silicone gel sheet	Patient preference, change in scar width + height, mean time to symptomatic relief	More patients preferred silicone gel over TAC. Silicone gel had shorter average time to improvement compared with TAC	Low
Taheri, 2019	10	46	(Iran)	Laceration, surgical	≥1 year	NR	Botulinum toxin A	Modified VSS	Botulinum toxin A reduced various parameters of the mVSS	Med
Van Der Wal, 2010	23/46	38 (18–69)	(Netherlands)	Burn	N/A	NR	Topical silicone gel	POSAS, DermaSpectrometer	Topical silicone gel significantly improved the surface roughness of burn scars and patients experienced significantly less itching, however, did not lead to a greater overall improvement when compared to placebo	Med

Table 1 *Continued*

Author, year	($n^{\dagger}$)	Mean age (years)	Ethnicity (study site[‡])	Scar aetiology	Scar duration	Lost to F/U	Treatment arms	Outcomes used	Key findings	Risk of bias
Verhaeghe, 2013	22	41	Caucasian, Asian	Surgical, trauma	N/A	NR	NAFR	PhGA, PGA, POSAS	Blinded PhGA could not confirm the clinical efficacy of 1540-nm non-ablative fractional laser, but the treatment is safe, and patients judged that the treated part had a better global appearance	Med
Wagner, 2010	21	16–79	(Germany)	NR	>1 year	NR	Er:YAG, silicone gel	Modified VSS (redness, elevation, hardness)	Er:YAG laser treatments (thermal and combined thermoablative mode) were effective for reduction of hypertrophic scars and keloids. However, silicone gel was not as effective	High
Wahba, 2019	45	20–45	(Egypt)	Burn	2–4 months	NR	Phonophoresis + silicone gel, phonophoresis + topical onion extract, corticosteroid phonophoresis	VSS	Silicone gel phonophoresis is a more effective method for the treatment of post-burn hypertrophic scars than onion gel phonophoresis or corticosteroid phonophoresis	Med
Wigger-Albert, 2009	55	38.2	(Germany)	NR	>6 weeks	12	Polyurethane, silicone dressing	Per cent change in overall scar index (SI)	Per cent change in scar index was comparable between silicone sheet (29.4%) and polyurethane (33.7%)	Low
Wittenberg, 1999	20	49	(USA)	Surgical	2.67 years	NR	PDL, silicone gel sheeting	Blood flow, elasticity, volume, pruritus, pain, burning	Improvements in scar sections treated with silicone gel sheeting and pulsed dye laser in dark-skinned patients were not different than the controls	Med

†(n) denotes number of participants with hypertrophic scars (where data are available); number following forward-slash (/) indicates total number of scars (if multiple scars per participant). ‡Study site provided where participant ethnicity not explicitly stated. 5-FU, 5-fluorouracil; Er:YAG, erbium laser; FCO_2, fractional CO2 laser; GAS, global assessment score; HDTA, high-density treatment arm; IPL, intense pulsed light; LDTA, low-density treatment arm; MSS, Manchester Scar Scale; mVSS, Modified Vancouver Scar Scale; NAFR, non-ablative fractional resurfacing; NdYAG, neodymium-doped YAG laser; NR, not reported; PDL, pulsed dye laser; PhGA, Physician Global Assessment; POSAS, Patient and Observer Scar Assessment Scale; SD, standard deviation; TAC, triamcinolone acetonide; VAS, visual analogue scale; VSS, Vancouver Scar Scale.

Table 2 Results of included studies by intervention and outcome measure

Author, year	*n*	Treatment arm	Follow-up period (months)	Outcome measure used	Mean values before (±SD)	Mean values after (±SD)*	Side effects
TAC							
Ali, 2016	14	Intralesional TAC	1	Efficacy (50% reduction in scar size)	N/A	5/14	Skin atrophy, hypopigmentation, telangiectasias, skin ulceration
Kelemen, 2008	12	Intralesional TAC	3	VSS	10	6	None reported
Khalid, 2019	60	Intralesional TAC	3	Height	3.547 ± 0.8730	1.894 ± 1.0751	Skin atrophy, telangiectasia, hypopigmentation, re-occurrence
				Efficacy (50% reduction in scar height)	N/A	58.80%	
Omranifard, 2007	40	Intralesional TAC + pressure garments	12	VSS	8.9 ± 1.9	6.7 ± 1.6	N/A
Sproat, 1992	14	Intralesional TAC	3	Patient preference	N/A	2/14 prefer TAC	N/A
				Time to symptomatic relief	N/A	6.8 ± 1.86	
				Change in scar width (cm)	N/A	*−0.25*	
				Change in scar height (cm)	N/A	*−0.13*	
Wahba, 2019	15	Intralesional TAC + phonophoresis	6	VSS	10.73 ± 1.27	8 ± 1.3	N/A
5-FU							
Ali, 2016	15	Intralesional TAC + 5-FU	1	Efficacy (50% reduction in scar size, no complications)	N/A	10/15	Skin atrophy, hypopigmentation, telangiectasias, skin ulceration
Khalid, 2019	60	Intralesional TAC + 5-FU	3	Height	3.665 ± 0.5777	1.144 ± 0.4717	Telangiectasia, ulceration, hyperpigmentation, re-occurrence
				Efficacy (50% reduction in scar height)	N/A	76.00%	
Laser therapy							
Al-Mohamady, 2016	11	PDL	1	VSS	6.6	3.1	Pain, purpura, hyperpigmentation
	11	NdYAG	1	VSS	6.6	1.5	Pain, bullae
Alster, 1998	20	FCO_2	3	GAS	1	2.4 ± 0.7	Erythema
	20	FCO_2 + PDL	3	GAS	1	3.2 ± 0.8	Erythema
Azzam, 2015	12	FCO_2	6	VSS	7.7 ± 1.3	4.4 ± 2.4	N/A
Choi, 2014	13	Er:YAG	10	VSS	8.3	6.1	Mild–moderate pain, erythema, oedema
	10	FCO_2	10	VSS	6.7	3.4	Mild–moderate pain, erythema, oedema
Daoud, 2019	23	IPL + FCO_2	6	MSS	13	7.8	None reported
	23	FCO_2	6	MSS	12.5	8	None reported

Table 2 *Continued*

Author, year	*n*	Treatment arm	Follow-up period (months)	Outcome measure used	Mean values before (±SD)	Mean values after (±SD)*	Side effects
Lin, 2011	10	High-density NAFR	3	Patient evaluation (% improvement)	N/A	*48 ± 10%*	Erythema, exfoliation, pain
				Blinded observer evaluation (3-point)	N/A	*2 ± 0.2%*	
	10	Low-density NAFR	3	Patient evaluation (% improvement)	N/A	*75 ± 10%*	Erythema, exfoliation, pain (to a lesser extent than in high-density arm)
				Blinded observer evaluation (4-point)	N/A	*2 ± 0.2%*	
Mehran, 2019	30	FCO_2	3	VSS	7.1 ± 2.3	5.6 ± 1.7	None reported
Omranifard, 2007	40	PDL	12	VBS	9.2 ± 1.7	4.2 ± 1.6	N/A
	40	Er:YAG	12	VBS	9.1 ± 1.7	4.6 ± 1.9	N/A
Ouyang, 2018	28	FCO_2	3	VSS	10.25 ± 0.80	3.50 ± 1.48	N/A
	28	PDL	3	VSS	10.29 ± 0.66	4.46 ± 1.50	N/A
Radmanesh, 2019	35	PDL	1	VSS	7.31 ± 1.93	4.33 ± 1.70	N/A
	35	FCO_2	1	VSS	7.31 ± 1.93	4.26 ± 1.48	N/A
Verhaeghe, 2013	22	NAFR	3	PhGA	N/A	Improvements in 10/18	Hyperpigmentation, scarring, erythema, oedema, burning, crusts, purpura, vesicles
Wagner, 2011	5	Er:YAG (thermal mode)	NA	mVSS (0–3)	Redness	(1.6 ± 0.24), Elevation (1.20 ± 0.20) Hardness (1.60 ± 0.24)	Redness (0.40 ± 0.24) Elevation (0.20 ± 0.20) Hardness (0.60 ± 0.24)
		Mild pain, redness, turgor, scabs	5	Er:YAG (combined thermoablative mode)	NA	mVSS (0–3)	Redness (1.40 ± 0.60) Elevation (1.40 ± 0.51) Hardness (1.80 ± 0.37)
Redness (0.40 ± 0.24) Elevation (0.60 ± 0.24) Hardness (1.25 ± 0.63)		Mild pain, redness, turgor, scabs	Microneedling				
Mehran, 2019	30	Microneedling	3	VSS	6.63 ± 1.95	3.8 ± 2.3	None reported
Surgical revision							
Jensen, 2018	25	Surgery + EXC 001	6	100 mm VAS	N/A	30.7 ± 13.55	Incision-site erythema, urinary tract infection, keloid scar
				POSAS (physician)	N/A	3.6 ± 1.43	
				POSAS (patient)	N/A	4.1 ± 2.48	
	25	Surgery	6	100 mm VAS	N/A	56.7 ± 22.56	Incision-site erythema, urinary tract infection, keloid scar
				POSAS (physician)	N/A	6.0 ± 1.70	
				POSAS (patient)	N/A	6.5 ± 2.93	
Silicone gel							
Harte, 2009	15	Silicone + pressure garments	6	VSS	7.181 ± 2.638	4.0 ± 2.323	N/A
Karagoz, 2009	15	Silicone	6	VSS	9.5 ± 0	4.4 ± 1.4	None reported
	15	Silicone gel sheet	6	VSS	10.0 ± 2.1	4.8 ± 2.1	Skin maceration, pruritus

Table 2 *Continued*

Author, year	n	Treatment arm	Follow-up period (months)	Outcome measure used	Mean values before (±SD)	Mean values after (±SD)*	Side effects
Kelemen, 2008	12	Silicone	3	VSS	10	6	None reported
Li-Tsang, 2006	24	Silicone + massage	6	Scar thickness	6.12 ± 0.17	4.17 ± 0.17	N/A
Li-Tsang, 2010	24	Silicone	6	VAS (pain)	1.61 ± 2.26	0.10 ± 0.45	N/A
				VAS (pruritus)	3.61 ± 2.88	1.05 ± 1.31	
				Scar colour (redness)	9.33 ± 2.77	8.35 ± 1.99	
				Scar thickness	5.76 ± 1.68	4.25 ± 0.95	
	29	Silicone + pressure garments	6	VAS (pain)	1.88 ± 2.34	0.33 ± 1.04	N/A
				VAS (pruritus)	4.35 ± 3.01	1.86 ± 3.09	
				Scar colour (redness)	8.49 ± 2.30	7.07 ± 1.53	
				Scar thickness	6.39 ± 2.31	4.02 ± 0.98	
Momeni, 2009	38	Silicone	4	VSS	9.37	4.17	None reported
Song, 2018	30	Silicone	3	VSS	N/A	3.9 ± 1.1	Pruritus
Sproat, 1992	14	Silicone	3	Number of patients preferring silicone	N/A	11/14	N/A
				Mean time to symptomatic relief (days ± SE)	N/A	3.9 ± 0.62	
				Change in scar width (cm)	N/A	*−0.125*	
				Change in scar height (cm	N/A	*−0.12*	
Van Der Wal, 2010	23	Silicone	12	POSAS (physician)	4.5	3	N/A
				POSAS (patient)	5.05	3	
Wahba, 2019	15	Silicone + phonophoresis	6	VSS	10.26 ± 1.22	3.86 ± 0.91	N/A
Wagner, 2011	3	Silicone + Er:YAG (thermal mode)	N/A	mVSS (redness, elevation, hardness 0–3)	Redness 2.33 ± 0.33 Elevation 1.67 ± 0.33 Hardness 2.33 ± 0.33	Redness 1.33 ± 0.67 Elevation 1.00 ± 0.58 Hardness 1.33 ± 0.67	Redness, turgor, scabs
	8	Silicone + Er:YAG (thermoablative mode)	N/A	mVSS (redness, elevation, hardness 0–3)	Redness 2.13 ± 0.23 Elevation 1.75 ± 0.31 Hardness 1.88 ± 0.35	Redness 1.38 ± 0.32 Elevation 1.13 ± 0.30 Hardness 0.88 ± 0.23	Redness, turgor, scabs
Wigger-Albert, 2009	55	Silicone	3	Overall scar index (SI)	26.7 ± 9.4	19.2 ± 9.5	Local dermatitis
Polyurethane dressing							
Wigger-Albert, 2009	55	Polyurethane dressing	3	Overall scar index	27.7 ± 9.1	18.7 ± 9.0	None reported
Massage therapy							
Cho, 2014	80	Massage + silicone gel + intralesional steroid + whitening cream + anti-redness cream + moisturising oil	N/A	VAS (pain)	5.63 ± 1.47	3.02 ± 0.81	N/A
				VAS (pruritus)	2.73 ± 0.88	1.56 ± 0.59	
				Scar thickness	0.28 ± 0.14	0.2 ± 0.9	
Li-Tsang, 2006	21	Massage	6	Scar thickness	6.12 ± 0.17	6.16 ± 0.25	N/A

Table 2 *Continued*

Author, year	*n*	Treatment arm	Follow-up period (months)	Outcome measure used	Mean values before (±SD)	Mean values after (±SD)*	Side effects
Li-Tsang, 2010	30	Massage + pressure garment	6	VAS (pain)	2.28 ± 0.78	2 ± 2.79	N/A
				VAS (pruritus)	4.78 ± 3.35	3.09 ± 2.34	
				Scar colour (redness)	8.56 ± 2.09	7.05 ± 1.65	
				Scar thickness	6.07 ± 2.70	4.49 ± 1.59	
	21	Massage	6	Scar colour (redness)	8.13 ± 1.49	7.96 ± 1.78	N/A
				Scar thickness	6.20 ± 1.98	6.7 ± 2.76	
				VAS (pain)	1.42 ± 2.47	1.36 ± 1.74	
				VAS (pruritus)	4.47 ± 2.45	2.63 ± 1.91	
Pentoxifylline							
Isaac, 2010	10	Pentoxifylline injection	1.25	Maximum oral opening	45.36 ± 0.9	3.25 ± 0.2	Pain from injections
				Dental distance	45.89 ± 0.72	4.19 ± 0.27	
				Patient satisfaction	N/A	8.8/10	
				Pain	N/A	4.4/10	
Botulinum toxin							
Taheri, 2019	5	Botulinum toxin type A	6	mVSS	10	9	N/A
				Blinded observer evaluation (4-point improvement scale)	N/A	*2 ± 0.2%*	
Topical Therapy							
Hedayatyanfard, 2018	20	Losartan Ointment	6	VSS	8	6	None reported
Mohammadi, 2018	30	Enalapril 1%	6	Mean size	N/A	2.02 ± 0.55	N/A
				Itching score	N/A	1.73 ± 0.69	
				Thickness	N/A	N/A	
Pressure therapy							
Harte D, 2009	15	Pressure garments	6	VSS	7.272 ± 2.149	4.818 ± 2.136	N/A
Lai, 2010	25	Low-pressure garment (10-15 mmHg)	5	Scar thickness	5.1 ± 1.07	*−19.7%*	Degradation of interface pressure
				Scar colour (redness)	110.68 ± 63.96	*−27.6%*	
	28	High-pressure garment (20-25 mmHg)	5	Scar thickness	4.94 ± 0.90	*−40.0%*	Degradation of interface pressure
				Scar colour (redness)	98.00 ± 49.38	*−55.4%*	
Combination therapy							
Cho, 2014	80	Silicone gel + intralesional steroid + whitening cream + anti-redness cream + moisturising oil	N/A	Scar Thickness	0.26 ± 0.15	0.26 ± 0.15	N/A
				VAS (pain)	5.65 ± 1.48	4.47 ± 1.34	
				VAS (pruritus)	2.78 ± 0.86	2.00 ± 0.70	
Onion extract gel therapy							
Karagoz, 2009	15	Onion extract gel	6	VSS	9.4 ± 1.4	6.1 ± 1.4	None reported
Song, 2018	30	Onion extract gel	3	VSS	NA	3.8 ± 1.4	Pruritus
Wahba, 2019	15	Onion extract gel + phonophoresis	6	VSS	10.46 ± 0.99	6.06 ± 1.09	N/A
No treatment							
Azzam, 2015	12	No treatment	6	VSS	7.6 ± 2.9	7.6 ± 2.9	–
Daoud *et al*, 2019	23	No treatment	6	MSS	11.5	11	–

Table 2 *Continued*

Author, year	*n*	Treatment arm	Follow-up period (months)	Outcome measure used	Mean values before (±SD)	Mean values after (±SD)*	Side effects
Hedayatyanfard, 2018	17	No treatment	6	VSS	8	8	–
Isaac, 2010	8	No treatment	1.25	Maximum oral opening (mm)	44.80 ± 1.36	0.66 ± 0.2	–
				Dental distance (mm)	43.86 ± 1.22	0.32 ± 0.41	
Mohammadi, 2018	30	No treatment	6	Mean size	N/A	2.30 ± 0.64	–
				Itching score	N/A	2.43 ± 0.67	
				Thickness	N/A	N/A	
Momeni, 2009	38	No treatment	4	VSS	9.09	5.68	–
Song, 2018	30	No treatment	3	VSS	N/A	5.4 ± 1.1	–
Van Der Wal, 2010	23	No treatment	12	POSAS (physician)	4.5	3	–
				POSAS (patient)	5.05	3	
Taheri, 2019	5	No treatment	6	mVSS	11	11.5	–

Bolded (*n*) indicates split-scar study. Italicised values denote percentage changes or overall changes in outcome score (when no means provided). 5-FU, 5-fluorouracil; Er:YAG, erbium laser; FCO_2, fractional CO_2 laser; GAS, global assessment score; IPL, intense pulsed light; MSS, Manchester Scar Scale; mVSS, Modified Vancouver Scar Scale; NAFR, non-ablative fractional resurfacing; NdYAG, neodymium-doped YAG laser; PDL, pulsed dye laser; PhGA, Physician Global Assessment; POSAS, Patient and Observer Scar Assessment Scale; SD, standard deviation; TAC, triamcinolone acetonide; VAS, visual analogue scale; VSS, Vancouver Scar Scale.

Silicone

Silicone was evaluated in 15 studies.[18,22,27,29–31,33,34–41] Compared to placebo, silicone products improved the surface roughness and pruritus of burn scars but did not significantly decrease the overall patient or physician measured POSAS scores compared with placebo.[40] Silicone led to better improvement for all elements of VSS except pain (55% *vs* 38% improvement in overall VSS score) in a half-scar study.[38] When topical silicone gel was compared with sheets, both were equally effective in lowering VSS scores (54% reduction for gel *vs* 52% reduction for sheets) and superior to onion extract gel, which yielded a 35% decrease in overall VSS score.[35] Wahba and colleagues [28] also showed a greater reduction in VSS scores in patients treated with silicone and phonophoresis *vs* those treated with onion extract and phonophoresis (62% *vs* 42% decrease in overall VSS score). However, silicone gel and onion extract gel were equally effective in reducing overall VSS and other scale scores.[39]

In a study of 67 patients, silicone gel sheets were inferior to polyurethane dressing in decreasing the scar index, a measure of colour, matte, contour, distortion and texture (29% *vs* 34%).[41]

Topical therapies

Topical losartan (an angiotensin II receptor antagonist) and enalapril (an angiotensin converting enzyme inhibitor) were evaluated in two studies. Losartan ointment reduced VSS, mainly vascularity and pliability, by an additional 20% compared with placebo.[42] Enalapril-treated scars were smaller in size and had lower itch scores compared with placebo scars after 6 months of treatment.[43]

Other treatments

Pressure garments were evaluated in two studies. High-pressure garments (20–25 mmHg) were found to be better at reducing scar thickness (40% *vs* 20%) and redness (55% *vs* 28%) compared with low-pressure garments (10–15 mmHg).[44] The addition of silicone to pressure therapy did not improve treatment efficacy.[34]

Massage therapy was evaluated in three studies. Silicone gel sheeting with lanolin deep massage resulted in significant reduction of thickness (32%) and pliability (35%) compared with lanolin deep massage alone.[36] The combination of silicone gel sheeting, pressure therapy and lanolin deep massage showed the greatest improvement in scar thickness compared with each treatment given as monotherapy.[37] Burn rehabilitation massage therapy combined with standard therapy led to a greater degree of improvement in pain (46%, $P < 0.001$) and pruritus (43%, $P < 0.05$) than standard therapy alone.[45]

Microneedling was evaluated in one study. At 3-month follow-up, microneedling improved VSS scores by nearly 43% ($P < 0.05$).[46] When compared to FCO_2 laser, microneedling resulted in a 2-fold greater improvement in VSS scores and showed better patient satisfaction.[46]

Figure 2 Risk-of-bias assessment of included studies.

Adverse events

Of the 34 studies included in this review, 14 reported adverse events (AEs) following their respective interventions (Table 2). Laser treatments were associated with pain, oedema, erythema and hyperpigmentation.[15,17,20,22–24] The most common AEs associated with TAC were telangiectasia (24%), hypopigmentation (20%) and skin atrophy (18%).[26,33] When TAC was combined with 5-FU, telangiectasia and hypopigmentation decreased to 3.5% and 5.3%, respectively.[25] Pentoxifylline injection was associated with injection-site pain.[31] Following EXC001 injection, erythema was reported in 12% as well as reported cases of keloid formation.[32] Most studies reported no AEs associated with silicone gels or sheets, although local dermatitis (3%),[41] skin maceration and pruritus have been reported.[35]

Risk of bias assessment

Of the 34 studies included, 11 studies scored low, 6 studies scored medium, and 17 scored high on overall risk of bias (Fig. 2). The studies were subdivided into those which performed an intention-to-treat (ITT) analysis (n = 15) and those which performed a per-protocol analysis (n = 19). Of the 15 studies with ITT analysis, only one study[39] was associated with a low risk of bias, while 5[18,23,28,30,40] and 9[17,20,25,29,31,33,35,37] studies were associated with moderate and high risk of bias, respectively.

To examine the possible impact of risk of bias on study results, effect sizes from studies with low risk of bias were compared with those from studies with high risk of bias. There was no correlation observed between risk of bias and effect size.

Meta-analysis

Of the 34 studies included in our review, VSS was the most commonly used outcome measure for scar assessment and was chosen for use in the meta-analysis. Seven studies examining the effects of TAC, laser, silicone and other therapies on VSS were included in the quantitative analysis. Silicone, laser and other treatments showed a 5.06 (95% CI: 6.78, 3.34), 3.56 (95% CI: 5.58, 1.54) and a 3.35 (95% CI: 4.58, 2.12) decrease, respectively, in the mean differences in VSS scores compared with no treatment (Fig. 3). Other treatments showed significant results only when microneedling, onion extract gel and pressure therapy were pooled under one category. Since only one study examined TAC, the data lacked power for meaningful comparison.

DISCUSSION

Our meta-analysis identified silicone, intralesional TAC, FCO_2 laser and PDL as efficacious treatment modalities for HTS in reducing VSS scores. When combined with silicone

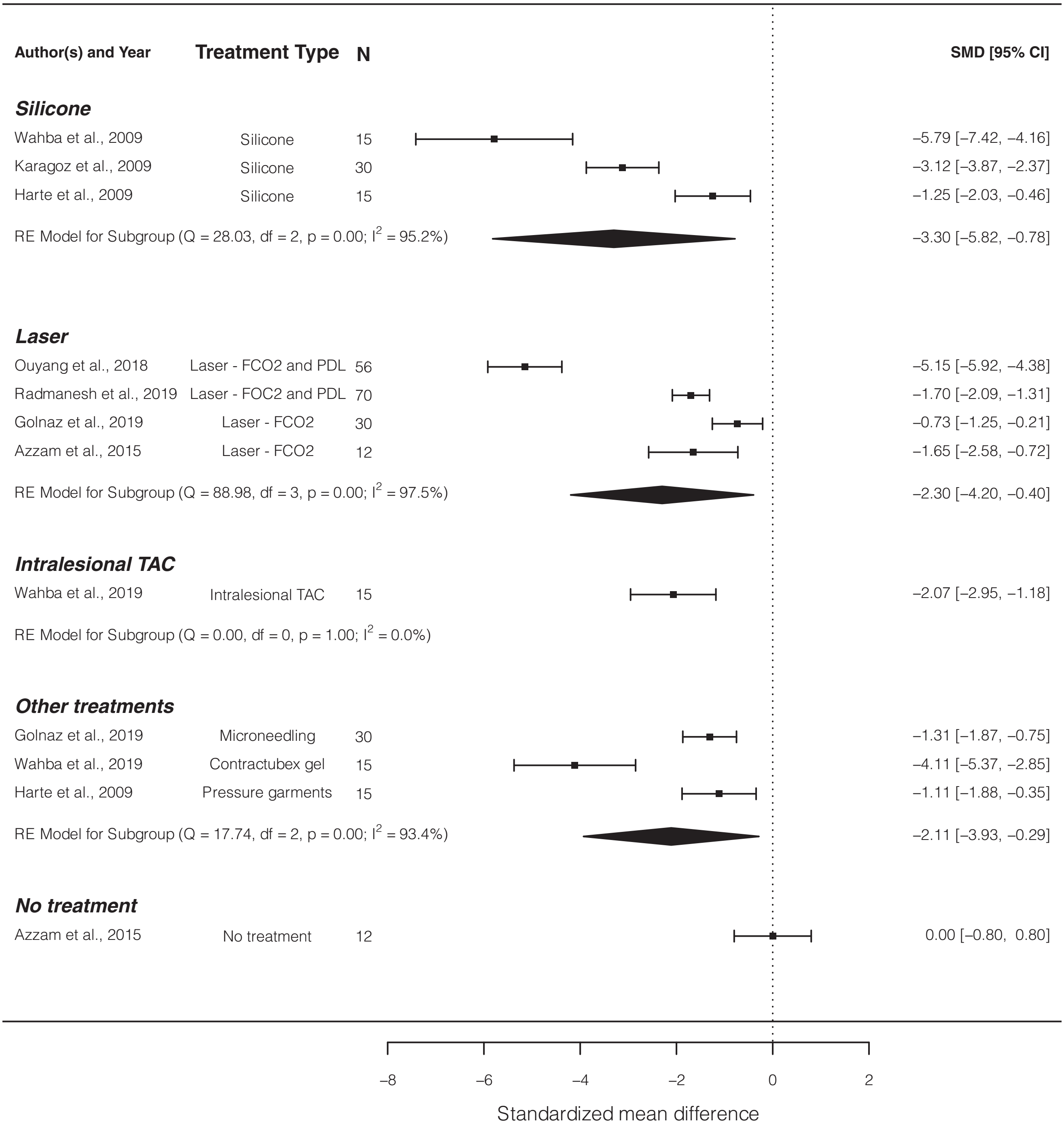

Figure 3 Meta-analysis of select studies reporting changes in Vancouver Scar Scale (VSS) (n = 7).

or 5-FU, intralesional TAC was more effective compared with intralesional TAC alone. The meta-analysis showed greatest efficacy for topical silicone, followed by laser, then other treatments utilising microneedling, onion extract gel and pressure therapy. The greatest magnitude of VSS decrease was reported with Nd:YAG laser (5.1), yet results were based on a single study which had a high risk of bias.[15]

The findings that highlight silicone, FCO_2 laser and PDL as some of the most effective treatment modalities for HTS are consistent with other guidelines and reviews.[6,7,47–49] However, previous studies note a higher rate of recurrence associated with FCO_2 laser.[7] Bao and colleagues[50] recommend TAC and 5-FU as first-line treatment for HTS and keloids, citing excellent outcomes, improved VSS scores and fewer adverse reactions compared to monotherapy with TAC, verapamil, cryotherapy, IPL, PDL, silicone or Nd:YAG laser. This is consistent with Kafka and colleagues [48] who also found the TAC and 5-FU combination to be superior to TAC, 5-FU, silicone gel sheeting and PDL. Nischwitz and colleagues[49] refrained from recommending a distinct treatment modality for hypertrophic scars due to heterogeneity of the studies included, but also highlighted the importance of TAC with 5-FU.

Further, evidence from studies included in our review indicates that massage in combination with silicone products is more effective than silicone alone. This is supported by evidence that manual massage reduces scar banding and pruritus as well as improving pliability.[51]

Our meta-analysis found greatest evidence for the use of silicone products in treating HTS. This is in contrast to Bao and colleagues and Kafka and colleagues, who found TAC in combination with 5-FU to be most effective. Additionally, Bao and colleagues examined treatment efficacy for both keloids and HTS, unlike our study which examined HTS only. The molecular differences between keloids and HTS may impact response to treatment.[52]

There are several limitations to this study. Most of the studies with the low risk of bias performed per-protocol analysis. Studies which did not use VSS to measure clinical outcomes or those which measured VSS but did not include mean before intervention, mean after and SD were not included in the meta-analysis, as studies with different outcome measures could not be compared meaningfully. A limitation of VSS is its disregard of patient-reported symptoms such as pain or pruritus.[53] Thus, our meta-analysis also does not comment on whether interventions help alleviate these parameters. For studies reporting the VSS as individual components, we could not combine the SD arising from each component and these studies were not included in the meta-analysis. The omission of studies during the meta-analysis reduces the generalisability of the study. To perform the meta-analysis, we pooled the results from different laser modalities including PDL, FCO_2 and Er:YAG into a single group which may have introduced heterogeneity. In addition, there can be significant heterogeneity even within the same group of lasers depending on the specific device, settings, number of treatments and treatment intervals. Similarly, we have pooled all forms of silicone including topical gel and sheeting under one category. We found significant heterogeneity ($I^2 = 95.6\%$), which can be explained by the diverse range of the interventions and patient demographics in the studies included in our review. Differences in duration, mechanism and location of scar, Fitzpatrick skin type, wound tension, method of closure, skin handling, postoperative scar management, duration and regimen of treatment modalities and duration of follow-up are additional sources of heterogeneity. Although several studies examining bleomycin, cryotherapy, imiquimod, shave or deep excision, and electrosurgery were identified in the search process, they were not included in the systematic review or meta-analysis as they did not meet inclusion criteria. As there are no clear guidelines on defining clinically significant improvement in scar healing, we have reported the per cent improvement of each intervention. Further studies are required to determine a consensus definition of clinical improvement.

CONCLUSION

In this review, we examined various HTS treatment regimens and found the most evidence for silicone, TAC in combination with silicone or 5-FU, and laser therapies, particularly FCO_2 laser and PDL therapies. Our meta-analysis based on studies utilising the VSS found silicone products to have the highest level of efficacy in reducing vascularity, pliability, pigmentation and height. Silicone had the lowest incidence of side effects, with 3–7% of patients experiencing temporary dermatitis. Further studies are needed to examine the efficacy of existing and emerging treatment modalities for HTS in order to facilitate the creation of up-to-date and evidence-based guidelines.

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Supporting Information

Additional Supporting Information may be found online in Supporting Information:

Table S1 The Vancouver scar scale.
Table S2. Search terms used for Medline.
Table S3. Search terms used for Embase.
Table S4. Search terms used for Web of Science.