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REVIEW ARTICLE

Excision and adjuvant treatment to prevent keloid recurrence. – a systematic review of prospective, clinical, controlled trials

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ABSTRACT

Keloids are defined as the formation of collagen-rich scar tissue extending beyond the original lesion. Not all keloids respond to conventional treatment with intralesional triamcinolone injections. Recurrence of keloids after primary excision is reported in almost 100% of cases and should therefore always be followed by adjuvant treatment. Currently, consensus on preferred adjuvant treatment in relation to keloid excision is lacking. This study seeks to systematically review evidence on the efficacy of adjuvant treatments in relation to keloid excision. A systematic literature review was conducted on PubMed. Titles, abstracts, and articles were screened and sorted according to defined inclusion- and exclusion criteria. Each study was evaluated according to the Oxford Centre for Evidence-Based Medicine, OCEBM, Levels of Evidence by two independent authors. Seven studies were eligible. Adjuvant treatment methods included intralesional triamcinolone injection, radiotherapy, silicone gel, pressure therapy, verapamil hydrochloride and 5-fluorouracil. While all the included studies reported promising results, two studies showed that minimizing dosages when treating with radiotherapy or triamcinolone should be considered to avoid adverse events. However, a high risk of bias was found in all the included studies.

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Keloid; adjuvant; excision; recurrence; scar

Introduction

Keloids are defined as hyperproliferative scars that extend beyond the borders of the initial wound [1–3]. Predisposition to keloid development has been reported for Fitzpatrick skin type [4–6]. Keloids are often located on the head and the upper part of the truncal region [7]. Pain, tenderness, and itching of the keloids are often the patient's main complaints [5,8]. Histologically, keloids are characterised by both increased fibroblast density and proliferation rates as well as thick wavy collagen fibres [9,10]. Keloids often appear during the healing process after an injury or inflammatory process of the skin but might not occur until months after the initial incident. The aetiology of keloids is still somewhat unknown, but several hypotheses have been proposed to explain keloid formation and growth [11,12]. Al-Attar et al. [13] list possible etiologies to keloid formation, including abnormal changes in growth factor activity, dysregulated collagen equilibrium, and misalignment of collagen fibres due to tension during the healing process. If left untreated, most keloids do not regress spontaneously. The conventional first-line treatment for keloids is triamcinolone injections [14]. For therapy resistant keloids, triamcinolone injections may be insufficient and require surgical intervention. Surgery alone leads to recurrence in up to 100% of cases [2,8,15], and evidence suggest that it should be followed by an adjuvant treatment [16]. However, there are examples of cases where keloid excision does not lead to recurrence [17]. Examples of possible adjuvants after keloid excision include intralesional triamcinolone injection, radiotherapy, brachytherapy, silicone gel or sheets, cryotherapy, pressure therapy, verapamil hydrochloride, 5-fluorouracil, imiquimod 5% cream and platelet-rich plasma [18–38]. There are few systematic reviews and none exclusively including prospective controlled studies examining the effects of adjuvant treatments in relation to keloid excision. This study aims to systematically review the current literature on prospective controlled trials of adjuvant treatments in relation to keloid excision supported by an evaluation of the methodological quality of included studies.

Methods

A systematic PubMed search was conducted in June 2020 to identify relevant clinical articles addressing adjuvant therapy in relation to keloid excision. Adjuvant treatment considered in this systematic review included pre- intra- and post adjuvant treatment protocols in relation to keloid excision. Relevant key words and Message Subject Headings (MeSH) were used and the following search strategy was created (Appendix 1).

An information professional was consulted to ensure a comprehensive and adequate search string.

Inclusion criteria were *in vivo*, human, prospective, controlled studies of keloid excision in relation to an adjuvant treatment and studies written in English. Exclusion criteria were retrospective studies, case reports, and cohort studies, along with studies without excision, non-English studies, *in vitro* and animal studies.

The PubMed search yielded 309 titles. Two authors (JB and KK) independently screened all 309 titles, and, based on the inclusion- and exclusion criteria, seven studies were included (Figure 1). In the case of disagreement, the eligibility of the studies was resolved by discussion.

The methodological quality of the included studies was assessed for risk of bias according to The Cochrane Handbook for Systematic Reviews of Interventions [39].

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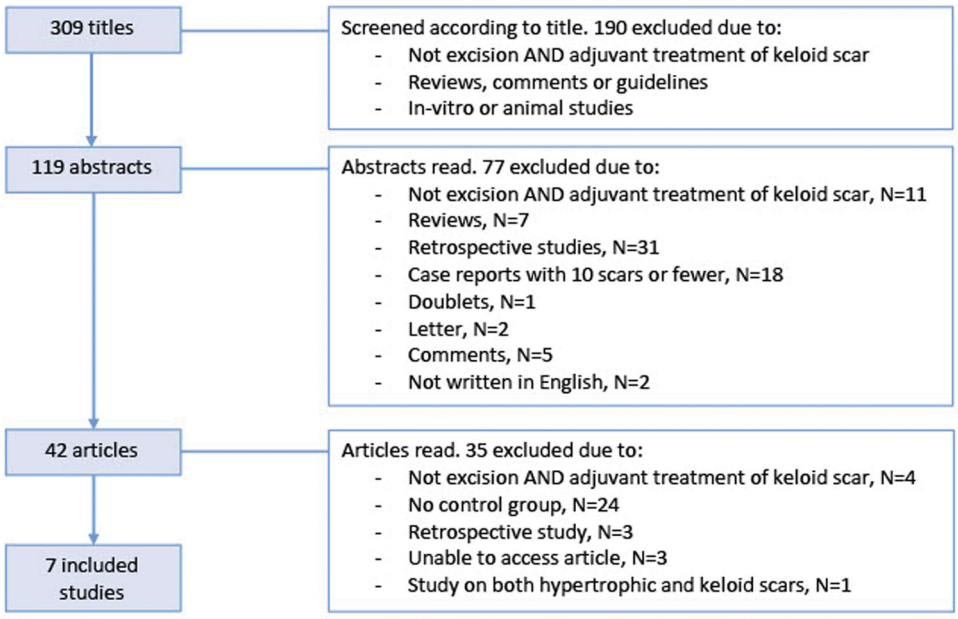

Figure 1. Flowchart of elimination process resulting in 7 included studies.

Two independent authors (JB and AH) performed the risk of bias assessment and the following four areas were addressed: (1) randomization, (2) allocation concealment, (3) blinding of outcome assessment, and (4) exclusion after randomization and loss to follow-up. The risk of bias was classified into three levels of risk: high, low, and unclear risk of bias.

The validity of the results was further addressed using the Oxford Center for Evidence-Based Medicine (OCEBM) Levels of Evidence [40–43].

Results

Seven studies met the inclusion criteria [18,21,23,24,26,28,30]. Table 1 gives an overview of adjuvant treatments in the seven included studies.

Publication dates ranged from 1996 to 2015. Sample sizes varied from 26 to 126 patients, some patients participated with more than one scar. Follow-up times ranged between 12 and 18 months.

Efficacy of adjuvant treatments after excision of keloids

Two studies were of similar structural design, having application of topical silicone sheets as the only adjuvant for the control groups and topical silicone sheets plus verapamil [28] or 5-fluorouracil [30] in the intervention groups. D'Andrea et al. [28] used five dosages of intralesional verapamil hydrochloride injections for their intervention group. They experienced full or partial recurrence in 45% of the cases in their intervention group and full or partial recurrence in 100% of the cases in the control group. Hatamipour et al. [30], on the other hand, used five doses of 5-fluorouracil as their second adjuvant for the intervention group. This study showed 25% of intervention cases experiencing full or partial recurrence, while 57% of cases in the control group experienced full or partial recurrence. Two studies compared two different methods for using radiation therapy as adjuvants. Li et al. [24] found a 16.7% recurrence rate when using their novel pre-cut, pre-radiotherapy method of administering radiation both before and after surgery, while the control group only received radiation after surgery with a recurrence rate of 55.6%. Ogawa et al. [26] compared high versus low dosage of radiation with reported recurrences of 4.1 and 4.3%, respectively. Two studies compared radiotherapy with triamcinolone injections. Sclafani et al. [21] compared various dosages of single-fraction radiation with two control groups. One control group was administered four injections of intralesional triamcinolone acetate, and the other, markedly smaller control group, was left without adjuvant treatment after excision of the keloid. This study found a 12.5% recurrence rate in the radiation groups and a 33% recurrence in both control groups. However, one of the control groups consisted of only 3 keloids. Emad et al. [18] compared superficial X-ray therapy with a control group treated with multiple sessions of cryotherapy plus intralesional triamcinolone acetonide injections. They found that radiation therapy yielded similar results compared to the control group, with a full or partial recurrence rate of 29.6 and 31.2%, respectively. Bashir et al. [23], compared the effects of a single intraoperative injection of triamcinolone with a triple injection protocol, consisting of one intraoperative and two postoperative injections of triamcinolone. In the one-injection group, a recurrence rate of 8.5% was recorded, while triple-injection yielded a reported recurrence rate down to 5.7%.

Patient satisfaction

Two studies included patient satisfaction as part of their major outcome measures. Patients in Li et al. [24] were given a questionnaire about their opinions but no detailed guidelines. Of the patients in the intervention group, 50.0% graded the aesthetic results as good, 41.7% as acceptable and 8.3% as poor, while in the control group, 20.7% of patients graded the aesthetic results as good, 31.0% as acceptable and 48.3% as poor. Emad et al. [18] also recorded patient satisfaction, but specifications about the collection of data are not included. In the intervention group, 89.5% were satisfied, 10.5% were partially satisfied, and none were unsatisfied. In the control group, 66.7% were satisfied, 22.2% were partially satisfied and 11.1% were unsatisfied. Findings are summarized in Table 1.

Table 1. Included studies on excision and adjuvant treatment to prevent keloid recurrence.

First author/last author, year (Study design)	OCEBM level of evidence	Number of patients (age)	Scar characteristics	Excision method	Intervention, number of scars = *N*	Control, number of scars = *N*	Major outcome measures	Follow-up	Adverse events	Major results
Sclafani/Romo, 1996 (RCT)	2b	31 Mean age = 28.1 (intervention = 27.3, control 1 = 29.4 control 2 = 27.0)	Location: ear lobe (27), ear lobe + helix (4)	Total excision by scalpel, wounds closed without tension	Single fraction radiation dosage of either 10 Gy, *N* = 8, or 7 Gy, *N* = 8, using superficial 100 kVp x-ray or electron beam within 3 h post-surgery. Application of Bacitracin 3 times daily for 10 days post-surgery	Control 1: intralesional 0.4 cc triamcinolone acetate, 40 mg/cc plus injection on postoperative days 7, 21 and 35. Application of Bacitracin 3 times daily for 10 days post-surgery, *N* = 12 Control 2: Application of Bacitracin 3 times daily for 10 days post-surgery, *N* = 3	Recurrence = 'any scar irregularity'	3 Months postoperatively, then every 6 months for a median of 18 months	None	Intervention recurrence: 2 (12.5%) Control 1 recurrence: 4 (33%) Control 2 recurrence: 1 (33%)
D'Andrea/Baroni, 2002 (CCT)	2a	44 Age range = 22–45	Location: back (*N* = 20), sternum (*N* = 12), deltoid (*N* = 12) Diameter = 2 − 6 cm Age = 2 − 5 years	Perilesional excision	Topical silicone sheets applied upon first sight of scar formation, lasting 6–9 months + intralesional 2.5 mg/ml verapamil hydrochloride injections immediately after operation and on day 7, 14, 28, and during second month post-surgery (dosages from 0.5 to 2.0 ml depending on keloid size), *N* = 22	Topical silicone sheets applied upon first sight of scar formation, lasting 6–9 months, *N* = 22	Recurrence = absence of result, improvement in size and consistence = partial result, keloid free = complete result	Postoperative day 28, in the second month, third month and lastly at 18 months	NA	Intervention: Absence of result = 2 (9%) Partial result = 8 (36%) Complete result = 12 (54%) Control: Absence of result = 18 (82%) Partial result = 4 (18%) Complete result = 0 (0%)

First author/ last author, year	Oxford level of evidence	Number of patients (age)	Scar characteristics	Excision method	Intervention, number of scars = N	Control, number of scars = N	Major outcome measures	Follow-up	Adverse events	Major results
Emad/Ghaem, 2010 (CCT)	2b	26 Mean age = 29.15 (intervention = 28.3, control = 30)	Location: trunk (41), upper limbs (15), lower limbs (8), ear lobe (8), scalp (1), neck (5)	Extralesional excision	Irradiation within 48 h after excision 12 Gy in 3 weekly fractions, given by a superficial X-ray therapy machine (120 kV, 10 mA, 2 mm A1 filtration, 4 mm A1 half-value layer), *N* = 44 (19 patients)	Multiple sessions (mean of 5.84 ± 2.51 sessions) of cryotherapy followed by intralesional, intradermal injection of 10 mg/ml of triamcinolone acetonide until flattening occurred or effect stagnated, *N* = 32 (9 patients)	Remission and patient satisfaction	Every 3 months for a minimum of 1 year, then semi-annually for another year (mean follow-up duration of 19 months)	Hyperpigmentation, hypopigmentation, ulceration + necrosis, telangiectasia, infection and wound dehiscence	Intervention remission: Full = 31 (70.4%) Partial = 5 (11.4%) Failure = 8 (18.2%) Control remission: Full = 22 (68.8%) Partial = 1 (3.1%) Failure = 9 (28.1) Intervention rating satisfaction: Satisfied = 17 (89.5%) Partially satisfied = 2 (10.5%) Unsatisfied = 0 (0.0%) Control rating satisfaction: Satisfied = 6 (66.7%) Partially satisfied = 2 (22.2%) Unsatisfied = 1 (11.1%)
Hatamipour/Shirazi, 2011 (RCT)	1b	47 Age range = 22–45	Location: sternum (*N* = 19), back and abdomen (*N* = 20), deltoid (*N* = 5) Diameter = 2 − 6 cm Age = 2 − 5 years	Perilesional excision	Topical silicone sheets applied upon first sight of scar formation (10–20 days), lasting 6–9 months + Intralesional injection of 50 mg/ml 5-flourouracil on postsurgical days 7, 14, 28 and during second and third months (dose from 0.6 to 1 ml depending on keloid size), *N* = 24	Topical silicone sheets applied upon first sight of scar formation (10–20 days), lasting 6–12 months, *N* = 23	Recurrence, partial improvement, no recurrence (keloid free)	Initiation of study, at 6 and 12 months	Commonly encountered side effects: pain at injections site, ulceration and burning sensation. No significant difference observed in the two groups	Intervention: Recurrence = 1 (4%) Partial improvemen *t* = 5 (21%) No recurrence = 18 (75%) Control: Recurrence = 5 (22%) Partial improvement = 8 (35%) No recurrence = 10 (43%) $\chi^2 = 5.63$ $df = 2$ $p < 0.05$

(*continued*)

Table 1. Continued.

First author/ last author, year	Oxford level of evidence	Number of patients (age)	Scar characteristics	Excision method	Intervention, number of scars = N	Control, number of scars = N	Major outcome measures	Follow-up	Adverse events	Major results
Li/Liu, 2013 (RCT)	2b	53 Mean age intervention = 21 ± 6 Mean age control = 23 ± 5	Location: chest wall, Mean size: 5.4 × 9.8 cm (control: 5.6 × 9.3 cm, Intervention: 5.2 × 10.3 cm)	NS, wound closed with split-thickness skin graft	Pre-cut method: incision to subcutaneous layer, closing of wound followed by radiotherapy within 24 h (9 Gy) After 10–14 days: second round of radiotherapy administered (9 Gy), $N = 29$	First round of radiotherapy on postoperative day 10–14, second round 7 days later (both 9 Gy), $N = 24$	Recurrence and aesthetic satisfaction (evaluated by patients)	6 and 12 months postoperatively	NA	Intervention recurrence: 16.7% Control recurrence: 55.2% $\chi^2 = 6.73$ $p < 0.01$ Intervention rating satisfaction as poor: 8.3% Control rating satisfaction as poor: 48.3% $\chi^2 = 7.50$ $p < 0.01$
Ogawa/Hyakusoku, 2013 (CCT)	2b	140	Location: earlobe	Wedge excision and primary suture	Radiation therapy using 4-MeV electron beam with a dose of 10 Gy delivered in two fractions over two days, starting one day post-surgery Patients advised to use taping fixation for 6 months, $N = 122$	Radiation therapy using 4-MeV electron beam with a dosage of 15 Gy, three fractions over three days, starting one day post-surgery Patients advised to use taping fixation for 6 months, $N = 47$	Recurrence	18 Months postoperatively	NA	Intervention: recurrence = 5 (4.1%) Control: recurrence = 2 (4.3%)
Bashir/Khan, 2015 (RCT)	1b	70 Age > 14 Mean age, intervention = 22.88 ± 4.22 Mean age, control = 22.34 ± 4.95	Location: helix Mean size, intervention = 2.61 ± 0.569 cm^2 Mean size, control = 2.54 ± 0.516 cm^2	Extralesional wedge excision that included cartilage and app. 1 mm of normal tissue. Small z-plasty added along free margin of helix	One intra-operative and two post-operative injections of triamcinolone 40 mg/cc (each with a dose of 0.5–1.0 cc), $N = 35$	Single intra-operative injection of triamcinolone 40 mg/cc (dose of 0.5–1.0 cc), $N = 35$	Recurrence (defined as development of hypertrophy)	Monthly follow-up for a minimum period of one year (12–16 months, mean of 17.44 ± 3.13)	Complications included hypo-pigmentation, telangiectasia, necrosis, ulceration and wound dehiscence. Intervention: complication rate = 8 (22.8%) Control: complication rate = 3 (8.5%) $p = 0.10$	Intervention: recurrence = 2 (5.7%) Control: recurrence = 3 (8.5%) $p = 0.64$

NA: not available; NS: not specified; RCT: randomized controlled trial; CCT: clinical controlled trial.

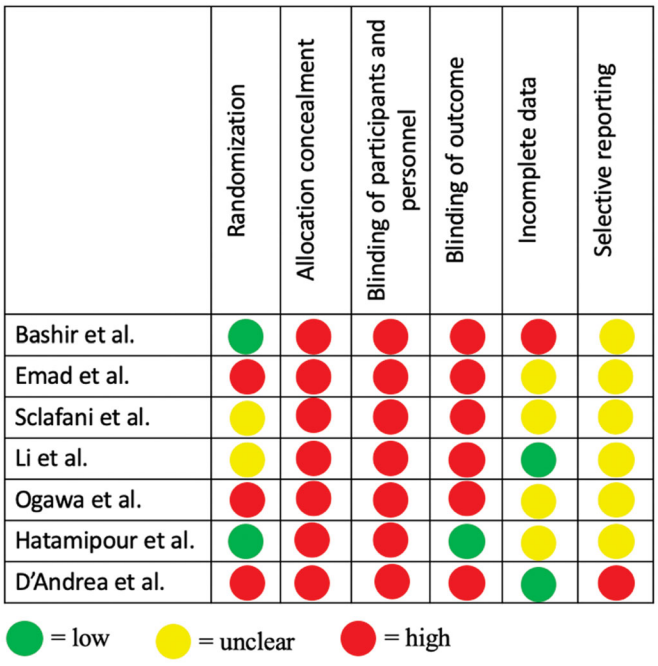

Figure 2. Methodological quality of included studies presented as assessment of risk of bias.

Risk of bias assessment

The evaluation of the methodological quality revealed a generally high risk of bias. Of the four studies claiming to be randomized, only one, Bashir et al. [23], provided a transparent and adequate randomization procedure, thus presenting a low risk of selection bias. Both Sclafani et al. [21] and Hatamipour et al. [30] had an unclear risk of bias with regards to randomization, as they did not describe the method of randomization. Li et al. [24] claimed randomization but described a method containing a high risk of bias. The three remaining non-randomized studies were all considered to have a high risk of bias. High risk of bias was also revealed with regards to 'allocation concealment', 'blinding of participants/personnel' and 'blinding of outcome', except in the case of Hatamipour et al. [30] who provided sufficient 'blinding of outcome'. In the 'incomplete data' category, only two studies presented a low risk of bias and one a high risk of bias.

The study with the highest methodological quality was performed by Hatamipour et al. [30]. Additional risk of bias was noted, but not included in the risk of bias table, in 3 studies [18,21,26] as they treated multiple keloids on some of the patients without taking into account the fact that regarding these results as being independent might manipulate the final outcome. Findings are summarized in Figure 2.

OCEBM levels of evidence

Using the OCEBM Levels of Evidence, each study has been individually assessed and given a grade ranging from 1 b to 2 b. The results can be seen in Table 1.

Discussion

This systematic review reports on the clinical effects of adjuvant treatment in relation to keloid excision. Included studies investigated the effect of the following adjuvants: radiotherapy, triamcinolone injections, cryotherapy, silicone sheets, verapamil hydrochloride injections, and 5-fluorouracil injections in various combinations in relation to the excision of keloid scars.

Sclafani et al. [21], Li et al. [24] and Ogawa et al. [26] found promising results when using radiotherapy as an adjuvant. Li et al. introduced a protocol of administering radiation therapy both before and after surgery. A similar approach has been investigated in scar prevention studies using lasers and supports the theory of affecting the cytokine response prior to excision in order to minimize scar formation [44,45]. Emad et al. [18] also used radiotherapy with good results, but experienced adverse reactions and unfavorable results compared with the control group, which showed equally good results but fewer side effects. However, due to heterogeneity in the study designs, a summary of the results does not allow for final conclusions. The noteworthy difference may be due to the different dosages of radiotherapy. While triamcinolone is already frequently used as adjuvant treatment in relation to keloid excision, Sclafani et al. [21], Emad et al. [18] and Bashir et al. [23] further substantiated claims on its efficacy. Interestingly, Bashir et al. [23] found similar results and fewer side effects when lowering the dosage of triamcinolone. Sclafani et al. [21] showed better results in using radiotherapy as an adjuvant when compared to both control groups. Finally, D'Andrea et al. [28] and Hatamipour et al. [30] used verapamil and 5-fluorouracil respectively. Both adjuvants in combination with silicone sheets appear to be favorable compared to only using silicone sheets as tested in the control group.

The results of the two studies measuring patient satisfaction, Emad et al. [18] and Li et al. [24], hold a high risk of bias as the participants were not blinded. There would have been a lower risk of bias had these evaluations been double-blinded.

We excluded retrospective and uncontrolled cohort studies, as the results of such studies should be treated with caution. Four of the included studies claimed to be randomized. Two of the reportedly randomized studies either lacked specification or noted a biased method of randomization and were thus considered to have an unclear risk of selection bias [21,24]. Hatamipour et al. [30] and Bashir et al. [23] both used less biased methods of randomization (ten randomized block design and random allocation of their patients into two groups using a computer-generated random number table, respectively). Whilst it is almost impossible to conduct a fully unbiased study design, patient allocation by random number generators and coin-flipping holds the least bias and is therefore preferable.

The studies included in this article have follow-up periods ranging from 12–18 months. Whether a keloid occurs right after an injury or several months later tends to vary [46,47]. The long-term effect of an adjuvant treatment combined with excision vs. excision alone may take even longer to evaluate than demonstrated in the included studies.

Skin type is a reported factor in the development of keloids, hence an analysis of skin type distribution would have been of interest. Only Sclafani et al. [21] report the distribution of skin types. Since it is still unknown why darker skin types are generally at a greater risk of keloid formation compared to lighter skin types, it would be relevant to examine if treatment response varies in dark and light skin types as well.

In general, the surgical methods, including excision margin, undermining, suture material, and technique, were not reported. However, Ogawa [26] did report on differentiating surgical methods according to lesion size and location. The surgical method alone may influence the keloid recurrence after excision and should be included in the description of the studies.

In only one study, Bashir et al. [23] provided sample size calculations. Thus, the remaining studies were unclear as to whether an adequate number of patients were included in order to make the results reliable.

With OCEBM grades ranging from 1 b to 2 b, the quality of evidence is sub-par and needs to be higher before any final conclusion can be made as to which is the most efficient adjuvant treatment to keloid excision. As a result, further research is very likely to change any conclusions drawn from these studies.

The strength of this systematic review is the extensive search string conducted on PubMed. Two independent authors used clearly-defined inclusion- and exclusion criteria, which led to the extraction of seven studies. A comprehensive search strategy consisting of relevant key-words and MeSH-terms was developed with the added expertise of an information professional. Two methods of evaluation were used to determine the quality of the included studies: 'risk of bias' and 'levels og evidence'. Both methods helped to disclose both the reliability and the confidence in the estimated effect reported in these studies.

The limitations of this study are the exclusion of non-English articles and the use of a single database. PubMed was, however, considered sufficiently comprehensive to cover relevant prospective controlled studies in this area.

Conclusion

Radiotherapy, triamcinolone, verapamil and 5-fluorouracil as adjuvants to keloid excision all showed promise to prevent recurrence. Furthermore, two studies showed that minimizing dosages when treating scars with radiotherapy and triamcinolone should be considered to avoid unnecessary side effects. However, the risk of bias was high in all studies. As confirmed by the level of evidence assessment and the high risk of bias, more studies of high quality are needed before standard protocols can be implemented for adjuvant treatment in relation to keloid excision.

In particular, double-blinded controlled trials with sufficient power to detect relevant differences along with elimination of risk of bias and longer follow-up periods should be attempted.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Appendix

('adjuvants, pharmaceutic'[Pharmacological Action] OR 'adjuvants, immunologic'[Pharmacological Action] OR 'adjuvants, pharmaceutic'[MeSH Terms] OR ('adjuvants'[All Fields] AND 'pharmaceutic'[All Fields]) OR 'pharmaceutic adjuvants'[All Fields] OR 'adjuvant'[All Fields] OR 'adjuvants, immunologic'[MeSH Terms] OR ('adjuvants'[All Fields] AND 'immunologic'[All Fields]) OR 'immunologic adjuvants'[All Fields] OR auxiliary[All Fields] OR additional[All Fields] OR extra[All Fields] OR supplementary[All Fields] OR supplemental[All Fields]) AND ('therapy'[Subheading] OR 'therapy'[All Fields] OR 'therapeutics'[MeSH Terms] OR 'therapeutics'[All Fields] OR 'treatment'[All Fields] OR 'treatments'[All Fields] OR 'excision'[All Fields] OR 'steroids'[MeSH Terms] OR steroids[Text Word] OR 'triamcinolone acetonide'[MeSH Terms] OR triamcinolone acetonide[Text Word] OR 'radiation'[MeSH Terms] OR 'radiation'[All Fields] OR 'radiations'[All Fields] OR 'electromagnetic radiation'[MeSH Terms] OR ('electromagnetic'[All Fields] AND 'radiation'[All Fields]) OR 'electromagnetic radiation'[All Fields] OR 'radiotherapy'[Subheading] OR 'radiotherapy'[All Fields] OR 'radiotherapy'[MeSH Terms] OR 'silicone gel'[All Fields] OR 'pressure'[MeSH Terms] OR ('pressure'[All Fields] AND earring[All Fields]) OR 'lasers'[MeSH Terms] OR 'lasers'[All Fields] OR 'laser'[All Fields] OR 'Radiation, Ionizing'[Mesh] OR 5-flourouracil[All Fields] OR 'Fluorouracil'[Mesh] OR 'interferons'[MeSH Terms] OR 'interferons'[Text Word] OR 'interferon'[Text Word] OR 'retinoids'[MeSH Terms] OR 'retinoids'[Text Word] OR 'retinoid'[Text Word] OR 'calcium channel blockers'[Pharmacological Action] OR 'calcium channel blockers'[MeSH Terms] OR ('calcium'[All Fields] AND 'channel'[All Fields] AND 'blockers'[All Fields]) OR 'calcium channel blockers'[All Fields] OR ('calcium'[All Fields] AND 'channel'[All Fields] AND 'blocker'[All Fields]) OR 'calcium channel blocker'[All Fields] OR 'cryotherapy'[MeSH Terms] OR 'cryotherapy'[All Fields] OR ('cold'[All Fields] AND 'therapy'[All Fields]) OR 'cold therapy'[All Fields] OR ('cold'[All Fields] AND 'therapies'[All Fields]) OR 'cold therapies'[All Fields] OR 'histamine antagonists'[Pharmacological

Action] OR 'histamine antagonists'[MeSH Terms] OR ('histamine'[All Fields] AND 'antagonists'[All Fields]) OR 'histamine antagonists'[All Fields] OR 'antihistamines'[All Fields] OR 'penicillamine'[MeSH Terms] OR penicillamine[Text Word] OR penicillamines[Text Word] OR 'colchicine'[MeSH Terms] OR colchicine[Text Word] OR 'bleomycin'[MeSH Terms] OR 'bleomycin'[Text Word] OR 'bleomycins'[Text Word] OR 'imiquimod'[MeSH Terms] OR 'imiquimod'[All Fields] OR 'cyclosporins'[MeSH Terms] OR 'cyclosporins'[All Fields] OR 'cyclosporine'[All Fields] OR 'cyclosporine'[MeSH Terms] OR 'cyclosporin'[All Fields]) AND ('keloid'[MeSH Terms] OR 'keloid'[All Fields])