ORIGINAL ARTICLE

Role of verapamil in preventing and treating hypertrophic scars and keloids

Ru Wang[1], Yu Mao[2], Zhenyu Zhang[1], Zhengyong Li[1], Junjie Chen[1] & Ying Cen[1]

1 Department of Burn and Plastic Surgery, West China Hospital of Sichuan University, Chengdu, China
2 Pediatric Department, The People's Hospital of Sichuan Province, Chengdu, China

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Abstract

Keloid and hypertrophic scars are difficult to manage and remain a therapeutic challenge. Verapamil has shown a great potential in the management of keloid and hypertrophic scars. Comparing with conventional corticosteroid injections, verapamil could improve the appearance of keloid and hypertrophic scars, and is associated with a lower incidence of adverse effects. Is verapamil an effective alternative modality in the prevention and treatment of keloid and hypertrophic scars? The aim of this study was to assess the effectiveness of verapamil in preventing and treating keloid and hypertrophic scars. Searches were conducted in Medline, EMbase and Cochrane databases from 1974 to January 2015. The selection of articles was limited to human subjects. Five randomised controlled trials (RCTs) or cluster-randomised trials or controlled clinical trials (CCTs) comparing the efficacy of verapamil with conventional treatments were identified. The results showed that verapamil could improve keloid and hypertrophic scars, and was not significantly different from conventional corticosteroid injections. Few adverse effects were observed. However, this result should be considered carefully, as most of the included studies have a high risk of bias because of issues with randomization, allocation concealment, blinding, incomplete outcomes and selective reporting. In conclusion, verapamil could act as an effective alternative modality in the prevention and treatment of keloid and hypertrophic scars. More high-quality, multiple-centre, large-sample (RCTs) are required to define the role of verapamil in preventing and treating keloid and hypertrophic scars.

Introduction

In clinical presentations, any abnormal wound healing will result in pathological scarring such as keloids and hypertrophic scars (1,2). Keloids are elevated fibrous scars that extend beyond the borders of the original wound, do not regress and usually recur after excision. Patients at high risk of keloids are usually younger than 30 years and often are Africans, Caucasians and Orientals. Histologically, keloids are characterised by large, thick collagen fibres, with few or even no myofibroblasts (3–5).

Hypertrophic scars are similar, but remain within the boundaries of the original wound and usually regress over time. Histologically, hypertrophic scars are characterised by the presence of small blood vessels and collagen fibres randomly distributed in small groups of nodules. The presence of myofibroblasts is common (3–5).

Key Messages

- verapamil can improve keloid and hypertrophic scars
- few adverse effects were observed using verapamil
- verapamil could act as an effective drug in the treatment of keloid and hypertrophic scars

They usually develop 3 months after the trauma. Symptoms such as erythema, itching, burning and pain may be present, and finally resulting in functional and cosmetic deformities, psychological stress and patient dissatisfaction (6,7). High-risk trauma includes burns, ear piercing and any factor that prolongs wound healing. Anterior chest, shoulders and upper arms, earlobes and cheeks are most susceptible to developing keloid and hypertrophic scars (8). They are difficult to treat, with a high recurrence rate.

First-line management of keloid and hypertrophic scars include silicone sheeting, pressure dressings and corticosteroid injections. Surgical removal poses a high recurrence risk unless combined with one or several of these standard therapies (8,9). Despite numerous proposed therapies reported in the literature, the management of keloid and hypertrophic scars is still challenging as there is no universally accepted treatment regimen (4,10). Currently, there are many approaches for preventing and treating keloids and hypertrophic scars.

Verapamil, a calcium channel antagonist, has been recommended in the management of keloids and hypertrophic scars because of its ability to decrease extracellular matrix production in scars (11−19). Intralesional verapamil injection (2·5−10 mg/ml, at timed intervals) has already been successfully used in the past for keloid and hypertrophic scars (15−18,20−22). Moreover, topical verapamil at a concentration of 50 μM is also an excellent choice as a scar modulator (23).

Verapamil is a calcium channel blocker that acts specifically on the L-type calcium channels present in the cell plasma membrane, blocking the influx of calcium from the extracellular matrix to the cytoplasm. By blocking the entrance of calcium into the cells, verapamil helps reduce the cytosolic concentration of this ion, inducing a series of morphological alterations and its functions (24,25).

Lee *et al.* (17) were the first to report the response of burn scars to intralesional verapamil. Nowadays, numerous studies have shown the role of verapamil in the management of keloid and hypertrophic scars. Verapamil could inhibit the synthesis/secretion of extracellular matrix, induce fibroblast procollagenase synthesis and inhibit IL-6, VEGF, TGF-β1 and cellular proliferation of fibroblasts, resulting in depolymerization of actin filaments, alteration of cell shape, apoptosis and reduction of fibrous tissue production (11,21,22,26−28).

Verapamil shows great potential for controlling the biosynthesis of its extracellular matrix, and has already been successfully used for treating keloid and hypertrophic scars. Recently, it is reported that verapamil can improve the appearance of keloid and hypertrophic scars, and have been associated with a lower incidence of adverse effects, compared with conventional corticosteroid injections (18,20). Is verapamil an effective alternative modality in the prevention and treatment of keloid and hypertrophic scars? More evidences are needed for making this clinical decision.

Therefore, in this study, we attempt to assess the effects of verapamil in preventing keloid and hypertrophic scarring in people with newly healed wounds of any type, and also evaluate the effects of verapamil in treating established scarring in people with keloid and hypertrophic scars after any type of wound.

Materials and methods

Inclusive criteria of published studies

Types of studies

We considered any randomised controlled trials (RCTs), cluster-randomised trials or controlled clinical trials (CCTs).
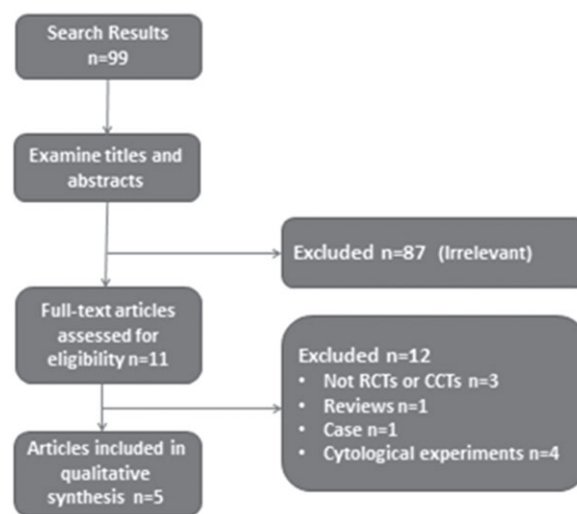

Figure 1 Flow diagram of the literature search and trials selection process.

Types of participants

People of any age with healed full-thickness wounds (damage to epidermis, dermis and subcutaneous tissue) where the skin is intact were included. Prevention studies that considered people with newly healed wounds and treatment studies that considered people with established scarring were considered.

Types of interventions

Comparisons of verapamil with all other conservative techniques (e.g. corticosteroids, silicon gel sheeting, 5-fluorouracil or no intervention) were considered eligible. We included comparisons of verapamil at different doses. We excluded any compound preparation containing verapamil.

Types of outcome measures

Primary outcomes. Prevention studies, including (i) recurrence (the number of people who develop keloid and hypertrophic scarring) and (ii) adverse reactions.

Primary outcomes. Treatment studies, including (i) change in scar size, measured by length, volume, height or width – usually by ruler or Vancouver Scar Scale (VSS) (ii) scar colour, by VSS or colour charts (iii) skin elasticity, measured serially with the use of an elastometer or VSS (iv) complications (e.g. rashes, atrophy, skin breakdown, pain measured on a numbered scale) (v) cosmesis as defined by patient opinion and physician observations (using assessment scales).

Secondary outcomes. (i) Quality of life; (ii) economic burden; (iii) others.

All of the studies involved in this study have been approved by the ethics committee, and the patients have signed their informed consent.

Search methods for identification of studies

An electronic search was conducted through the Medline, EMbase and Cochrane databases from 1974 to January 2015.

Table 1 Characteristics of the included studies

	Boggio (23)	Ahuja and Chatterjee (20)	Xu *et al.* (21)	Margaret Shanthi *et al.* (18)	D'Andrea *et al.* (15)
Population characteristics					
Subjects (*n*)	120 patients	40 patients (48 scars)	18 patients	54 patients	44 patients
Male:female	All females	Not specified	1:1	1:1	28:16
Mean age (years)	43	Not specified	Not specified	V:26, T:20	Not specified
Age (years)	31–65	15–60	12–48	10–50	22–45
Site of scar	Abdomen, breast	Pre-sternal, extremities, face, torso/back	Head, axilla, arm, pre-sternal, shoulder, abdomen	Face/neck, earlobe, sternum, abdomen/chest, limb	Back, sternum and deltoid
Scar duration	3 months	Under 2 years	1–1·5 years	Not specified	2–5 years
Cause of scar	Surgery	Post-infective, surgery, burns, trauma	Not specified	Burns, trauma, surgery, insect bite and acne	Not specified
Treatment history	Untreated	Untreated	Untreated	Not specified	Not specified
Intervention					
Duration (ms)	90 days	Until flattening or eight sessions	Not specified	Until flattened or 6 months	2 months
Dosage	50 µM	2·5 mg/ml, maximum 1·5 ml	2·5 mg/ml, 0·15 ml	2·5 mg, 1 ml	2·5 mg/ml, 0·5–2·0 ml
Frequency	Twice a day	Every 3 weeks	Once	Every 3 weeks	Four times
Treatments (*n*)	60	26 scars	6	27	22
Comparator	Placebo	Triamcinolone	IFN a-2b, triamcinolone, placebo	Triamcinolone	The same treatment except verapamil
Outcomes					
Primary outcomes	Stony Brook Scar Scale	Vancouver Scar Scale	PCNA, TGF-β1, Apoptosis	Vancouver Scar Scale	Recurrence
Study duration	3 months	24 weeks	7 days	1 year	18 months

The references of published studies were also reviewed for relevant articles. The search was limited to human subjects.

Data collection and analysis

Two review authors independently assessed the titles and available abstracts of all the studies identified during initial search and excluded any clearly irrelevant studies. They independently assessed the full-paper copies of reports of potentially eligible studies using the inclusion criteria. The authors resolved disagreements on inclusion by consensus and, when this failed, by arbitration by a third review author. Data were extracted by one review author and checked for accuracy by a second review author. We used a standard data form to capture the information. Data for prevention and treatment were dealt with separately. We requested additional unpublished data from primary authors and included when available.

For this review, two review authors independently assessed each included study using the Cochrane Collaboration tool for assessing risk of bias (29), which addresses random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other issues.

Statistical analysis

We allocated the results of the randomised controlled trial as dichotomous frequency data. Individual study relative risks (RRs) and 95% confidence intervals (CIs) were calculated from event numbers extracted from each trial before data pooling. Both fixed-effects and random-effects models were used to evaluate the pooled RR for verapamil treatment. All reported P values are two-sided, and P values of less than 0·05 were regarded as statistically significant for all the included studies. Statistical analyses were performed using STATA software (StataCorp LP, College Station, Texas) (version 10.0).

Results

Searches conducted in the Medline, EMbase and Cochrane databases yielded a total of 99 articles. After examining the titles and abstracts, 87 studies were excluded because they were irrelevant. Eleven full-text articles were assessed for further consideration. However, further seven articles were excluded (three were not RCTs or CCTs, one review, one case and two cytological experiments). Thus five trials were included finally, containing four English (two RCTs and two CCTs) and one Chinese (one CCT) (Figure 1) studies. Four trials compared verapamil injection with other treatments, and one trial compared verapamil gel with placebo. The included studies were conducted in four countries, and involved a total of 276 people aged 12 to 65 years. The controls included placebo, triamcinolone, interferon α-2b and topical silicone without verapamil injections. Two prevention studies and three treatment studies
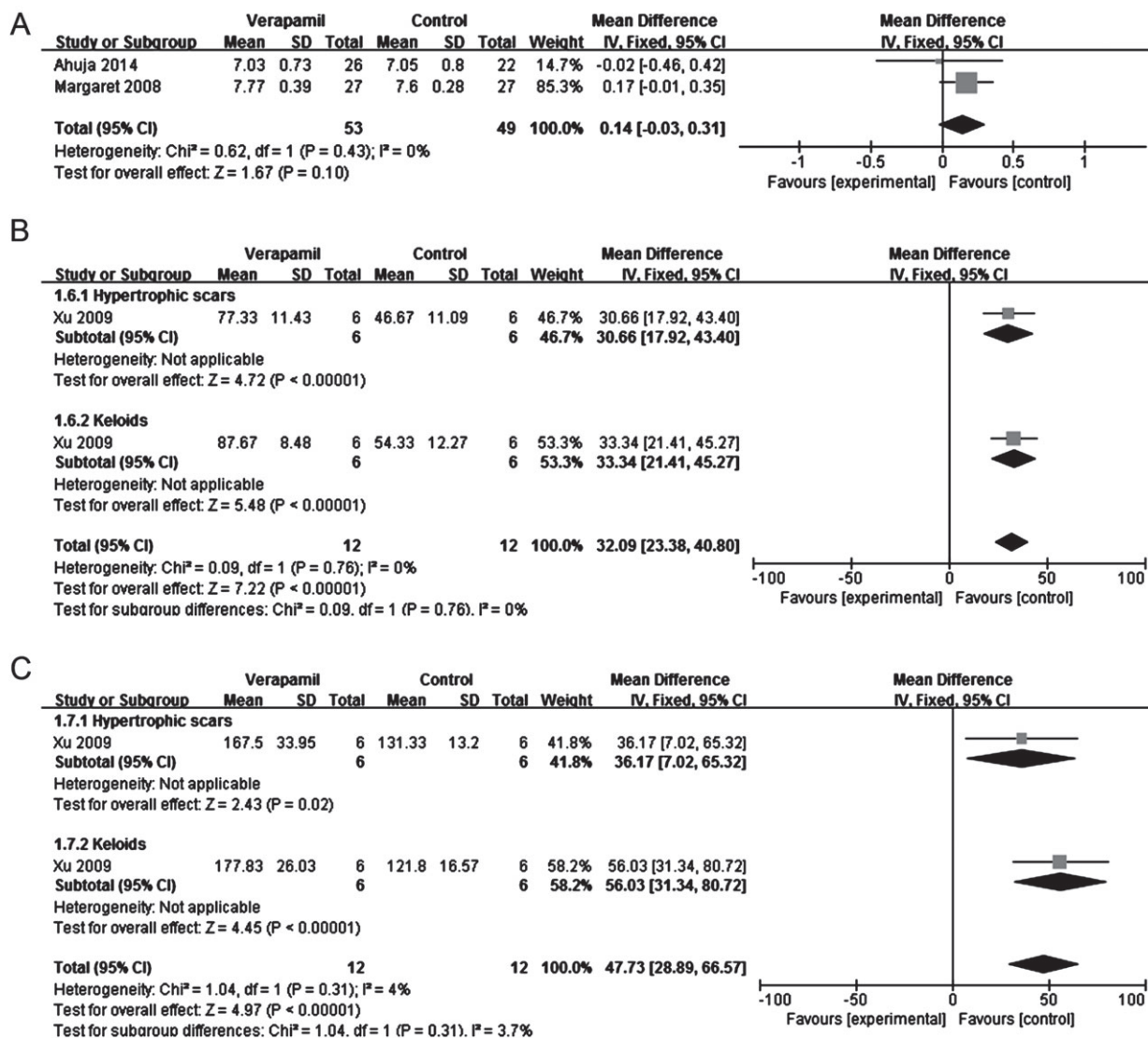
Figure 2 Forest plot of comparison: verapamil versus triamcinolone. (A) Mean difference in Vancouver Scar Scale. (B) Mean difference in TGF-β1 expression. (C) Mean difference in apoptosis.

were included. Characteristics of the included studies are shown in Table 1.

Verapamil compared with triamcinolone

Prevention studies

No prevention studies were identified.

Treatment studies

Two of the studies identified (involving 94 patients) used the VSS as the primary outcome (18,20). Mean zero VSS scores were achieved with treatments in respect of scar height, vascularity and pliability at 24 weeks in both trials. Reported data were treated as continuous and used mean difference. When both trials were pooled (fixed effect, $I^2 = 0\%$), there was no significant difference in the VSS in keloid and hypertrophic scars (mean difference = 0·14; 95% CI: −0·03 to 0·31) (Figure 2A).

But Margaret Shanthi *et al.* found that the rate of reduction in vascularity, pliability, height and width of the scar with triamcinolone was faster than with verapamil (18).

Xu *et al.* (21) compared the effects of intralesional triamcinolone with verapamil on TGF-β1 expression and apoptosis in vivo. After intralesional triamcinolone acetonide injection, TGF-β1 expression in keloid and hypertrophic scars could be significantly depressed (mean difference = 32·09; 95% CI: 23·38 to 40·80; fixed effect, $I^2 = 0\%$) (Figure 2B). But intralesional verapamil injection could induce apoptosis in both keloid and hypertrophic scars (mean difference = 47·73; 95% CI: 28·89 to 66·57; fixed effect, $I^2 = 3·7\%$) (Figure 2C) (21).

Verapamil compared with interferon α-2b

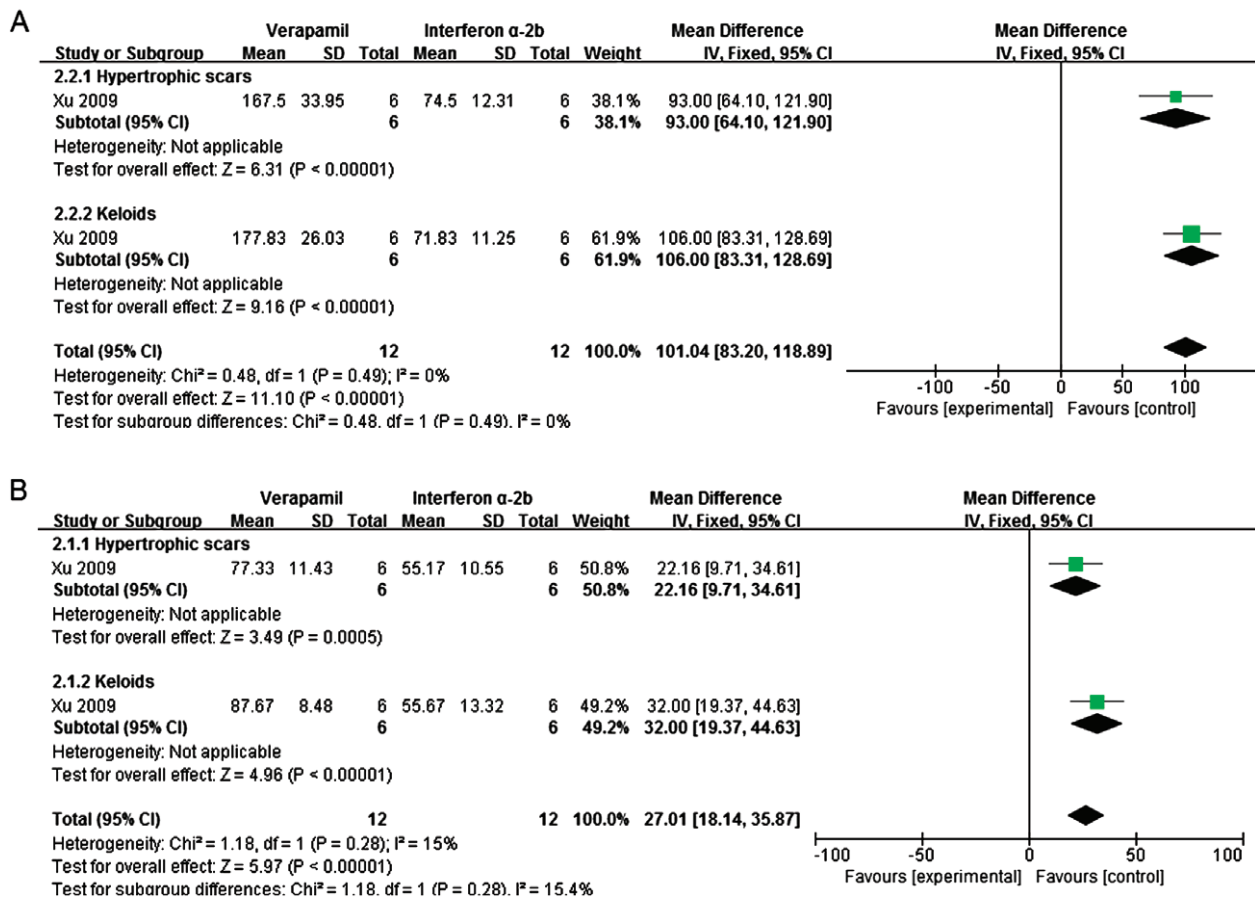### Prevention studies

No prevention studies were identified.

Figure 3 Forest plot of comparison: verapamil versus interferon α-2b. (A) Mean difference in apoptosis. (B) Mean difference in TGF-β1 expression.

Treatment studies

One study investigated the effects of intralesional interferon α-2b and verapamil on apoptosis and TGF-β1 expression in vivo. Verapamil could induce apoptosis in both keloid and hypertrophic scars (mean difference = 101·04; 95% CI: 83·20 to 118·89; fixed effect, $I^2 = 0\%$) (Figure 3A), but interferon α-2b could significantly prohibit TGF-β1 expression (mean difference = 27·01; 95% CI: 18·14 to 35·87; fixed effect, $I^2 = 15\%$) (Figure 3B) (21).

Verapamil compared with placebo

Prevention studies

Boggio *et al.* (22) compared topical verapamil (a nonionic gel containing verapamil at a concentration of 50 μM) with no treatment. The scars were rated using the Stony Brook Scar Evaluation Scale by blinded observers, and differences in the quality of the scars in patients who used verapamil compared with scars of those who did not use any healing modulator were significant ($P < 0.05$). Patients treated with verapamil presented good quality scarring (80% of mammoplasty scars and 75·2% abdominoplasty scars), while patients in no-treatment group showed 48% and 51·2% satisfaction for mammoplasty and abdominoplasty scars (23). The author was contacted for detailed data, but no response was received.

Treatment studies

One study reported the effects of intralesional verapamil injection and placebo on proliferation, apoptosis and TGF-β1 expression in vivo. Compared with no-treatment group, verapamil could inhibit fibroblast proliferation (mean difference = −52·17; 95% CI: −59·63 to −44·72; fixed effect, $I^2 = 39\%$) (Figure 4A), reduce TGF-β1 expression (mean difference = −20·49; 95% CI: −30·63 to −10·36; fixed effect, $I^2 = 0\%$) (Figure 4B) and induce apoptosis (mean difference = 100·45; 95% CI: 82·04–118·86; fixed effect, $I^2 = 0\%$) (Figure 4C) (21).

Verapamil + silicone compared with silicone

Prevention studies

Recurrence was investigated by D'Andrea *et al.* (15) as a primary outcome. In the first group, treated by perilesional surgical excision of keloids and topical silicone, combined with intralesional verapamil hydrochloride injection, keloids were cured in 54% of the cases. But in the control group, receiving the same treatment except the verapamil hydrochloride, no complete regression of keloids occurred (RR 0·47, 95% CI: 0·30–0·73). Furthermore, an amelioration of the lesion could be demonstrated in 36% of the cases in the first group, compared with 18% in the control group.
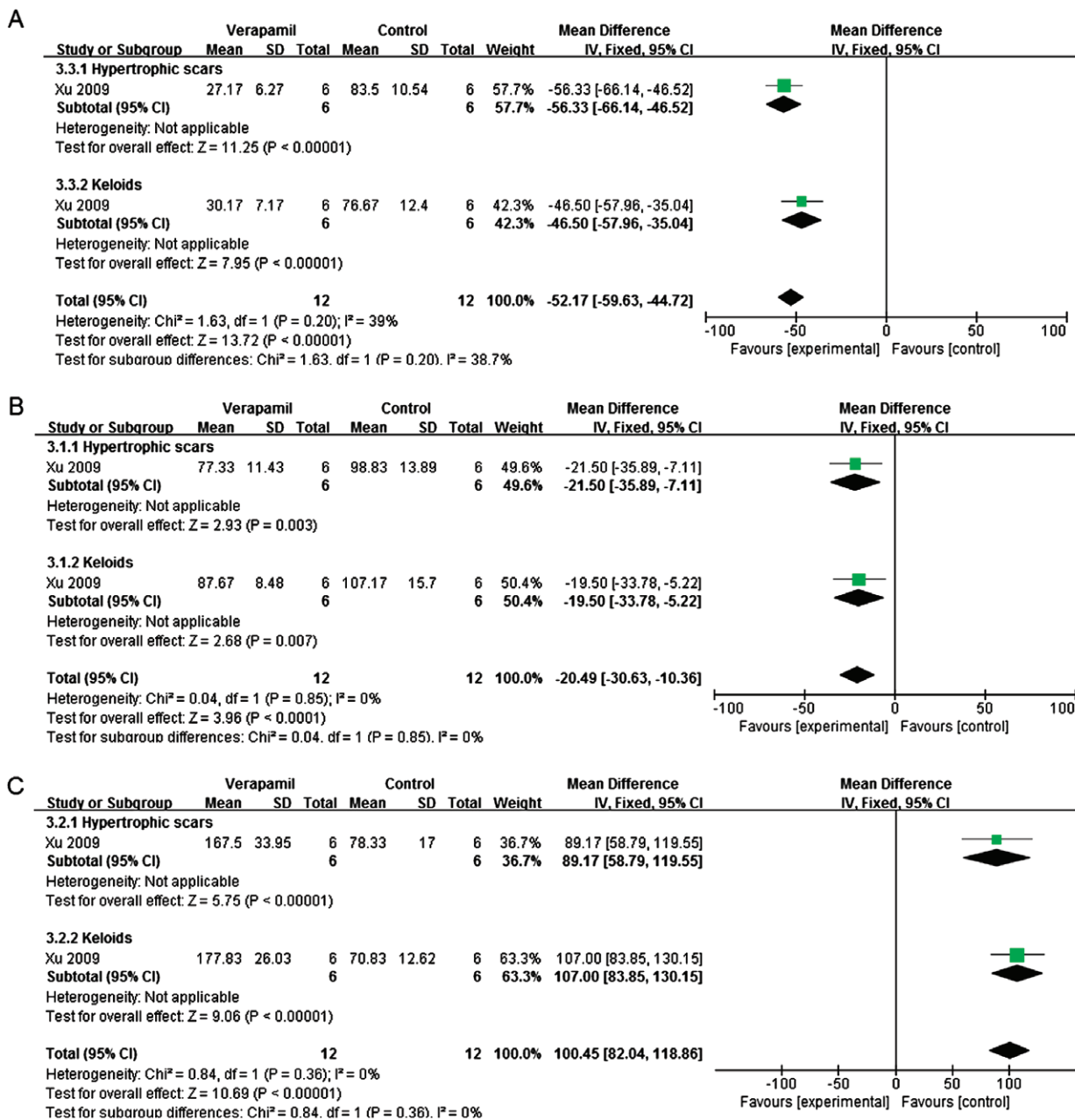
Figure 4 Forest plot of comparison: verapamil versus placebo. (A) Mean difference in fibroblast proliferation. (B) Mean difference in TGF-β1 expression. (C) Mean difference in apoptosis.

Treatment studies

No treatment studies were identified.

Complications

In the trial by Boggio *et al.* (23), there were no adverse reactions such as erythema, pruritus, or bullous lesions found in any of the cases after the use of topical verapamil.

Two trials reported that adverse drug reactions were more with triamcinolone than with verapamil (18,20). Only minor adverse effects (e.g. pain during injection of verapamil) were noted with verapamil (20).

Discussion

There were only two single-blind, randomised, controlled trials in the five included studies without allocation concealment, resulting in high risk of selection bias and performance bias. Therefore, the quality of the trials showed high risk of selection bias, probably affecting the outcomes reported (Table 2).

There were plenty of studies about verapamil for treating keloid and hypertrophic scars; however, some problems existed that made meta-analysis difficult. Firstly, the lack of a standardised protocol for keloid and hypertrophic scars, such as the duration of the scars, follow-up time, a standardised treatment protocol and assessment scale, made the synthesis of results

Table 2 Risk of bias

	Boggio (23)	Ahuja and Chatterjee (20)	Xu *et al.* (21)	Margaret Shanthi *et al.* (18)	D'Andrea *et al.* (15)
Random sequence generation	High risk	Low risk	High risk	Low risk	High risk
Allocation concealment	Unclear	Unclear	Unclear	Unclear	Unclear
Blinding	Low risk	Low risk	Unclear	Low risk	Unclear
Incomplete outcome data	Low risk	Low risk	High risk	High risk	Unclear
Selective reporting	Unclear	Unclear	High risk	Unclear	Unclear
Other bias	Unclear	Unclear	Unclear	Unclear	Unclear

and analysis difficult. Secondly, pathological scars, including hypertrophic scars and keloids, were clubbed together without subgroup analysis. Even morphologically similar hypertrophic scars differed pathologically and clinically from keloids (30,31). Therefore, the treatment details (e.g. dosage, frequency and duration) would be quite different. Thirdly, only figures were available in most articles and not original data, making it difficult to analyse data.

In summary, five RCTs or CCTs comparing the efficacy of verapamil with conventional treatments were identified (15,18,20,21,23,32). Results of the trials showed that verapamil could improve keloid and hypertrophic scars, and was not significantly different with conventional corticosteroid injections. Fewer adverse effects were observed.

However, this result should be considered carefully, as most of the included studies have a high risk of bias because of issues with randomization, allocation concealment, blinding, incomplete outcomes and selective reporting.

In conclusion, verapamil could act as an effective alternative modality in the prevention and treatment of keloid and hypertrophic scars. More high-quality, multiple-centre, large-sample randomised controlled trials are required to define the role of verapamil in preventing and treating keloid and hypertrophic scars.

Acknowledgements

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