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ORIGINAL ARTICLE
Reconstructive

Treatment of Keloids: A Meta-analysis of Intralesional Triamcinolone, Verapamil, and Their Combination

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Background: Keloids are skin lesions of abnormal and excessive scar proliferation that have no agreed upon gold standard of therapy. Extensive research in this area has shown that both intralesional triamcinolone and verapamil are effective in their treatment.

Methods: A review of these two treatment modalities was conducted via an extensive search of existing literature published in PubMed, Scopus Libraries, and Science Direct databases using keywords "keloid," "verapamil," "triamcinolone," "intralesional," "treatment," and "corticosteroid" published between 1996 and 2021. From these included studies, clinical trials that directly compared the effects of intralesional triamcinolone and verapamil from 2008 to 2021 were included in a meta-analysis. Lastly, the minimal current research pertaining to a potential future direction of their combination was described.

Results: Over 30 publications were included in this literature review to describe the current state of keloid treatment and outline the advantages and disadvantages of intralesional triamcinolone and verapamil. Eight of these studies were included in the meta-analysis which had varying results. In all studies, greater improvement was seen in the triamcinolone acetonide group compared with the verapamil group. However, these improved results were associated with a higher rate of adverse effects.

Conclusions: When comparing the modalities of triamcinolone acetonide and verapamil for keloid treatment, triamcinolone acetonide shows more significant and rapid improvement compared with verapamil; however, there are also increased adverse effects. Minimal combination studies of these treatments have shown that perhaps using them together can augment their mechanisms without the unwanted side effects. *(Plast Reconstr Surg Glob Open 2022;10:e4075; doi: 10.1097/GOX.0000000000004075; Published online 27 January 2022.)*

INTRODUCTION

Keloids are skin lesions of abnormal and excessive scar proliferation characterized by extensive collagen deposition and irregular fibrous tissue that extends beyond the margins of the original cutaneous injury. They are typically associated with pain and pruritus as well as a very high rate of recurrence. The exact mechanism of keloid formation is not fully understood, but it has been noted to occur due to various etiologies, including postsurgical, acne, burns, trauma, piercings, and inflammation. They can occur in many places on the body; however, the chest, shoulders, and earlobes are the most common locations.[1]

Although there are many treatment modalities in use, none have been determined to be the gold standard of care. Keloid therapy continues to be an emphasized area of research to attempt to find the best treatment possible. There have been numerous treatment modalities attempted in the clinical setting, ranging from noninvasive to surgical. These include pressure dressings, silicone gel sheeting, intralesional medications (corticosteroids, verapamil, bleomycin, 5-fluorouracil), topical mitomycin C, radiotherapy, cryotherapy, and excision.[2]

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Received for publication October 1, 2021; accepted November 29, 2021.

DOI: 10.1097/GOX.0000000000004075

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. This study received funding from Conrad and Caroline Jobst Foundation.*

Medical techniques generally aim to decrease fibroblast and extracellular matrix production by various mechanisms. Corticosteroids are effective in this way due to their ability to repress inflammation, which decreases fibroblast proliferation as well as glycosaminoglycan and collagen synthesis. Verapamil acts in the opposite direction by stimulating the production of collagenases to break down already formed collagen in keloid scars.[1] Because the development of keloid scars is considered a hypermetabolic state, it is comprehensible that antineoplastic drugs would be effective in this process. For example, bleomycin inhibits TGF-β1. Inhibiting this growth factor leads to decreased collagen production and apoptosis. Furthermore, 5-fluorouracil has been shown to cause increased fibroblast apoptosis and inhibit fibroblast proliferation. Mitomycin C also has beneficial antineoplastic effects that decrease fibroblast proliferation by way of suppressing DNA and RNA synthesis.[3]

Nonpharmacologic options include surgery, cryotherapy, and radiotherapy. Surgical techniques tend to be more popular, but also carry high rates of keloid recurrence especially when used as monotherapy.[4] The most effective cryotherapy technique has shown to be intralesional cryoneedle in which liquid nitrogen can be injected into a keloid. Lastly, radiotherapy has also been shown to be effective in preventing the recurrence of keloids. There are multiple delivery methods in use, including X-rays, electron beam, lasers, and brachytherapy.[5]

Seemingly, any single therapy treatment is not fully effective and is associated with high rates of recurrence. Various forms of combination therapies have become the mainstay; however, which combination becomes the question. Studied combinations include bleomycin + triamcinolone,[6] surgical intervention + verapamil,[7,8] hyaluronic acid + triamcinolone,[9] verapamil + triamcinolone,[10,11] triamcinolone + botulinum toxin,[12,13] surgical intervention + cryotherapy,[14] triamcinolone + 5-FU,[15] and many others.

This laundry list of therapy modalities has been studied extensively in clinical research. A common method of assessing the efficacy of these keloid treatments is with the Vancouver Scar Scale (VSS). This scale incorporates aspects of keloids, including vascularity, pigmentation, pliability, and height. The scoring is shown in Figure 1.

Studies have shown that treatment with intralesional triamcinolone and verapamil are both able to reduce vascularity, pigmentation, pliability, and height of keloid scars. These treatments are widely used and yet the question of which is superior still remains. The purpose of this meta-analysis was to investigate how intralesional triamcinolone compares to verapamil in the treatment of all patients with keloids, paying attention to adverse effects and efficacy in recent years, and to discuss potential future directions of their use. We did this by analyzing clinical trials that have directly compared their results. We also performed a literature review of PubMed, Scopus Libraries, and Science Direct databases from 1996 to 2021 to be able to adequately describe their mechanisms, efficacy, and side effects. Although other meta-analyses of this nature exist, ours goes further to describe a potential future direction of their combination.

Takeaways

Question: How effective are current keloid treatments, including intralesional triamcinolone and verapamil?

Findings: In a literature review and meta-analysis of clinical trials, better and faster results as well as increased adverse effects are seen when using triamcinolone for keloid therapy when compared with verapamil. Minimal combination studies of these treatments have shown possible augmentation of their mechanisms with less side effects.

Meaning: Intralesional triamcinolone and verapamil have both been effective in the treatment of keloids; furthermore, preliminary research of their combination has also yielded promising results.

VERAPAMIL MONOTHERAPY

Intralesional verapamil injections are able to stimulate the synthesis of collagenases in local tissue to increase the rate of collagen breakdown.[1,17] This effect is thought to be due to its ability to polymerize actin filaments, which changes the shape of fibroblast cells from elliptical to spherical.[18] Furthermore, verapamil has been shown to increase the production of decorin, which has multiple effects on fibroblasts, including decreased migration, proliferation, and increased apoptosis.[19] Specifically, verapamil decreases the production of IL-6 and vascular endothelial growth factor, which have previously been shown to be expressed in keloid fibroblasts.[20,21] Verapamil also inhibits the secretion of multiple substances that constitute the extracellular matrix such as glycosaminoglycans, fibronectin, and collagen.[21]These mechanisms combined result in decreased proliferation of fibroblasts and reduction of scar mass via apoptosis.

Multiple studies have been performed that support the efficacy of intralesional verapamil.[19,22–25] When combined with surgical excision, one analysis found a 54% cure rate and 36% of those with recurrence reported improvement in size.[22] Studies have also reported significantly decreased VSS scores post treatment.[19,24]

Some of the major benefits of verapamil treatment include simplicity and safety. Verapamil is consistently noted to have few minor side effects and no significant side effects when injected intralesionally. As discussed, keloids are commonly associated with both pain and pruritus. However, when calcium channel blockades are exhibited in excitable tissue, such as nerve fibers within keloids, they can slow the action potential and thus reduce the signaling of pain or pruritis.[20]

TRIAMCINOLONE MONOTHERAPY

Intralesional triamcinolone is effective in the treatment of keloids due to its ability to decrease inflammation, causing decreased collagen and glycosaminoglycan synthesis as well as collagen and fibroblast degradation.[1] Corticosteroids are also very effective vasoconstrictors. This is an advantageous effect in the treatment of keloids due to reduction of blood flow to the wound.[18]

Pigmentation	Vascularity	Pliability	Height
0 = normal	0 = normal	0 = normal	0 = normal/flat
1 = hypo-pigmentation	1 = pink	1 = supple	1 = > 0–1 mm
2 = mixed pigmentation	2 = red	2 = yielding	2 = > 1–2 mm
3 = hyperpigmentation	3 = purple	3 = firm	3 = > 2–4 mm
		4 = banding	4 = > 4 mm
		5 = contracture	

Fig. 1. Vancouver Scar Scale.[16]

Triamcinolone is commonly considered the first line therapy for keloid scars. Most clinical trials on this topic are comparing a new or less proven keloid treatment against the well known success of triamcinolone. Many studies have discussed its impressive and well-established efficacy.[18] One such trial reported a 97% reduction in mean VSS score from pretreatment to posttreatment.[24] An additional two studies have shown 100% decrease in scar height following treatment.[25,26] Furthermore, triamcinolone tends to have a rapid rate of improvement and an enhanced ability to decrease pain and pruritus commonly associated with keloids.[20] Although many studies have shown very promising results with triamcinolone injections, there is actually great variability in its efficacy when used as monotherapy. One meta-analysis of its use showed a 50%–100% range of regression rates and a 33%–50% recurrence rate.[27]

Although it is well agreed upon that triamcinolone is a powerful treatment for keloids, adverse effects are commonly associated with its use. Some studies have reported side effects in up to 91% of subjects.[20] Reported side effects with triamcinolone treatment include hypopigmentation or atrophy, telangiectasia, ulceration, menstrual abnormalities, and profuse sweating.[24,28] Some research has suggested that these side effects can be diminished with injections that are neither too deep or superficial.[1]

META-ANALYSIS: VERAPAMIL VERSUS TRIAMCINOLONE TRIALS

Introduction

Multiple clinical trials have been performed to comparatively analyze the results of intralesional verapamil and triamcinolone treatments.[1,7,18,20,24,26,29,30] We reviewed the results of these studies and combined data when appropriate to gain a more complete understanding of keloid etiologies, treatment efficacy, and adverse effects of these therapies.

Methods

Clinical studies were selected from PubMed, Scopus Libraries, and Science Direct searches from 1990 to 2021 using keywords "keloid," "verapamil," "triamcinolone," "intralesional," "treatment," and "corticosteroid." Studies were excluded due to not being primary research, not investigating the desired treatments and for not being performed on human subjects. We chose these parameters to better answer our research question and understand clinical outcomes in actual patients as opposed to animal models. Although there was no parameter to exclude by study type, all included studies were randomized controlled trials as no nonrandomized or observation studies of this nature were found. The exclusion and inclusion process is further detailed in Figure 2.

From these selected studies, we analyzed the keloid etiologies, the outcomes and efficacy, as well as reported adverse effects, as these factors are vital to patient satisfaction. Keloid etiologies were analyzed using a compiled average weighted for the amount of included subjects from studies that provided the necessary data. The clinical outcome of each treatment was measured using reported VSS scores, as this was the most common method in the trials and in keloid research overall. We analyzed VSS score data in two ways: total decrease in VSS score after treatment and percent decrease in score. The total mean decrease in VSS score for each treatment was able to be determined with the data given in five of the included studies. Either this was specifically reported by the study or the study reported VSS values before and after treatment for each of the four categories (pigmentation, vascularization, height, and pliability), and from that we pooled the SDs and extrapolated the total decrease in score with its 95% confidence interval. Then the weighted pooled variances were used to determine the total mean decrease in VSS score per treatment group with their respective SDs. A two variable unpaired *t*-test was then performed to determine if the outcomes were significantly different.

We also pulled the average percent decrease in VSS score from the appropriate studies that either reported this number or reported average before and after scores that a percent decrease could be determined from. From this data, we found an average percent decrease in score for each treatment that is weighted to the number of patients in each study so that patients across the studies were represented equally. Lastly, adverse reactions were analyzed using weighted averages from all studies that reported this data. We used this method to be able to look at all included patients information equally and

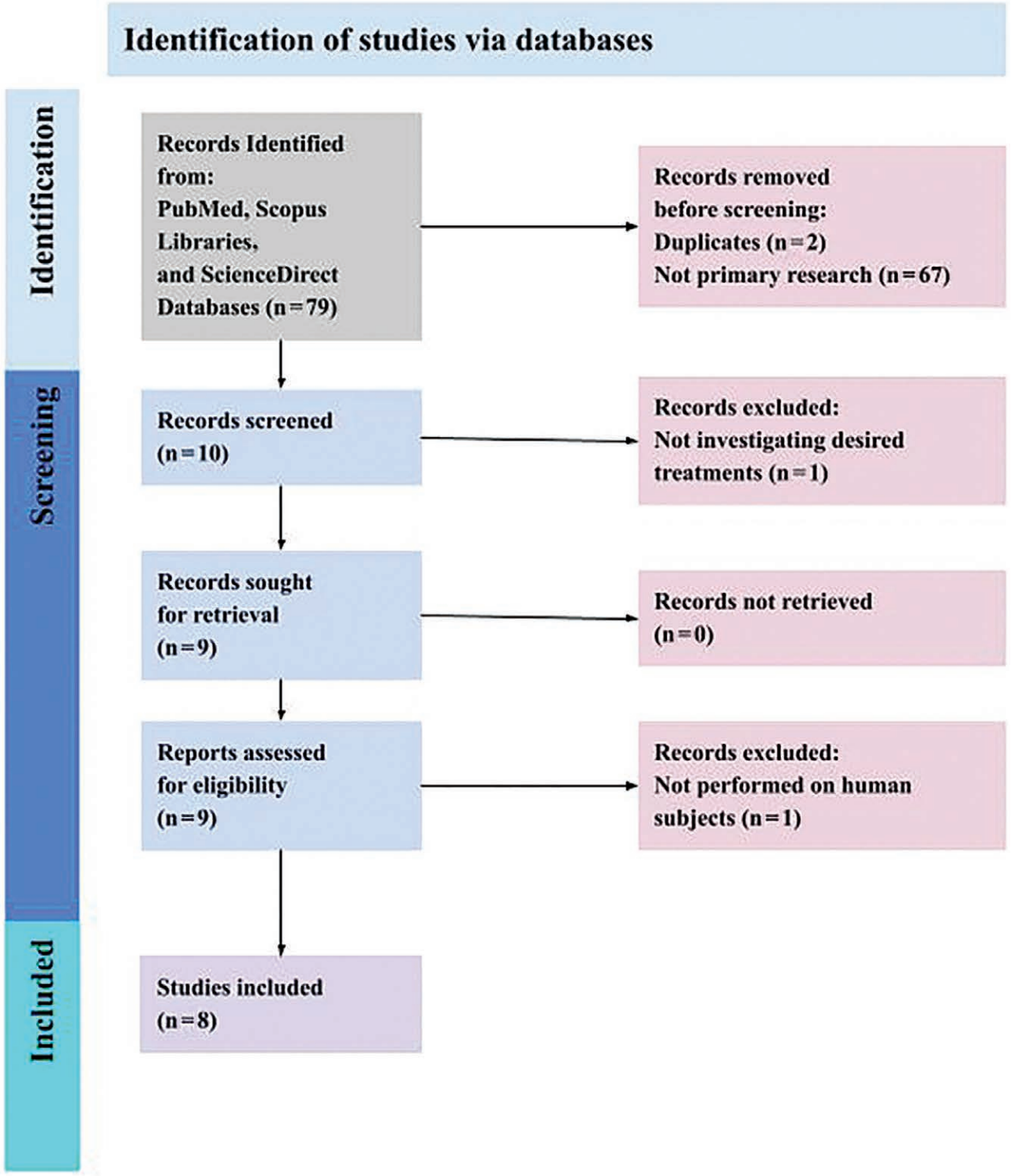

Fig. 2. Study inclusion and exclusion parameters PRISM diagram.

consistently to gain a larger understanding of these treatments in the clinical setting.

Results: Keloid Etiologies

Keloids are generally known to occur weeks to months following skin injury such as surgery, acne, burns, trauma, piercings, and inflammation. Five of the reviewed trials gave analysis on precipitating factors to keloid formation.[7,20,24,26,29] By compiling the data given on a total of 259 patients, we were able to determine that trauma was the most common initiating event followed by acne. The breakdown of etiologies within these 259 patients can be

visualized in Figure 3: trauma was the cause of 28% of keloids, acne accounted for 17%, 12% were determined to be spontaneous, 12% were due to furuncles/boils, ear piercing caused 7%, surgery scars encompassed 7%, shaving was 4%, vaccination injections were 3%, burns caused 3%, and other miscellaneous causes involved the remaining 7%.

Results: Outcomes and Efficacy

The included studies comparing the efficacy of triamcinolone and verapamil had varying results. Two concluded that Verapamil is not effective in the treatment of keloids.[26,30] Three had similar conclusions that although verapamil is effective, it is not as effective as triamcinolone.[1,7,20] The remaining three determined that verapamil and triamcinolone are equally as effective, but triamcinolone produces a faster rate of improvement.[20,24,29]

Figure 4 shows the average decrease in VSS score and its 95% confidence interval in each study for both treatment groups after 9–12 weeks of therapy as well as the average decrease in score when all five studies' results are pooled. As a greater decrease represents a better clinical outcome, it can be seen that more improvement occurred in the triamcinolone group as opposed to the verapamil group in all five studies and in their combination. Furthermore, an unpaired *t*-test with assumed equal variances (as determined by F-test) was performed with 310 degrees of freedom and a *t*-table value of 1.97 at an alpha level of 0.05. Because the calculated *t*-value was greater than the *t*-table value, at 16.19 > 1.97, it can be determined that the mean decrease in VSS score between the two treatment groups was significantly different with 95% confidence in the pooled data.

In Figure 5, the percent VSS score decrease for both treatments can be seen for each study as well as the compiled percent weighted mean decrease for all studies.[7,18,24,29,30] These statistical analyses and graphics all illustrate the same conclusion that intralesional triamcinolone is more efficacious than verapamil based on VSS scores.

Additionally, most studies reported that triamcinolone has a faster rate of recovery when compared with verapamil. Ahuja et al specifically described a faster improvement in scar height, vascularity, and pliability.[29] This could be due to the compositions of the two injections. Triamcinolone injections consist of benzyl alcohol, polysorbate, sodium carboxymethylcellulose, sodium chloride, and water. This mixture allows for a slower release of medication into the lesion. Alternatively, verapamil injections consist solely of sodium chloride as an excipient; therefore, it diffuses faster through the keloid and into the bloodstream as opposed to remaining in the area of interest.[20]

Results: Adverse Effects

Overall, verapamil is associated with fewer adverse effects and increased safety when compared with triamcinolone.[15] Seven of the eight included studies commented on the difficulty of adverse effects when treating keloids with intralesional triamcinolone. Belie et al reported that 32 of their 35 total patients (91.4%) experienced negative side effects with triamcinolone therapy. Comparatively, only two of the studies reported verapamil side effects and these tended to be more mild with a smaller incidence.

Verapamil side effects included headache and insomnia, whereas the adverse effects of triamcinolone included site atrophy, hypopigmentation, ulceration, and menstrual abnormalities. Five of the reviewed studies included data on adverse effects during their trial.[1,7,20,26,29] The average percentage of patients who experienced adverse effects was dramatically higher in the group treated with

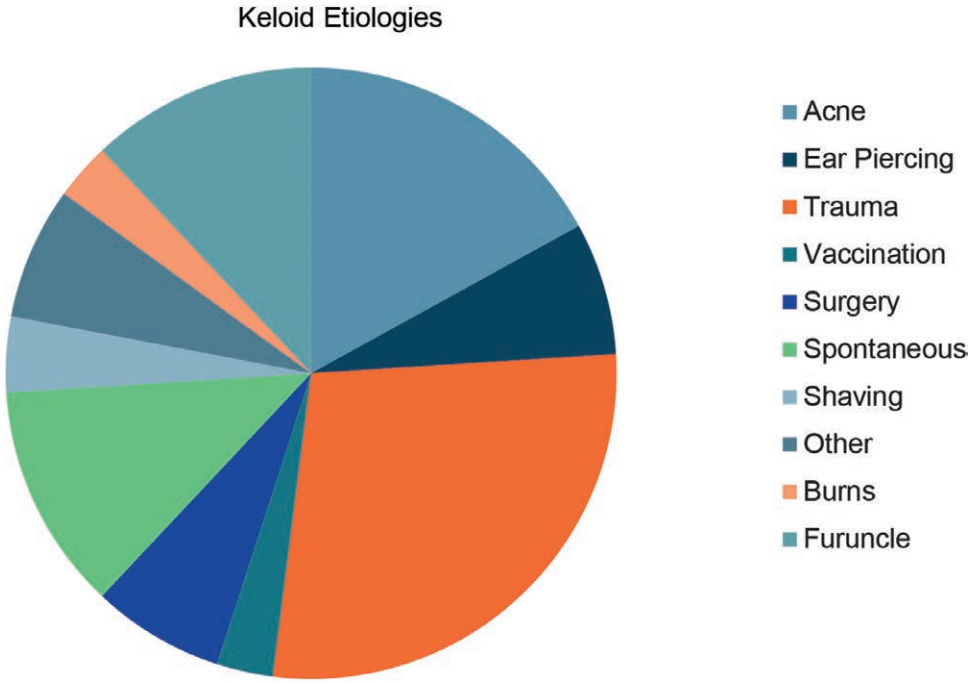

Fig. 3. Keloid etiologies.

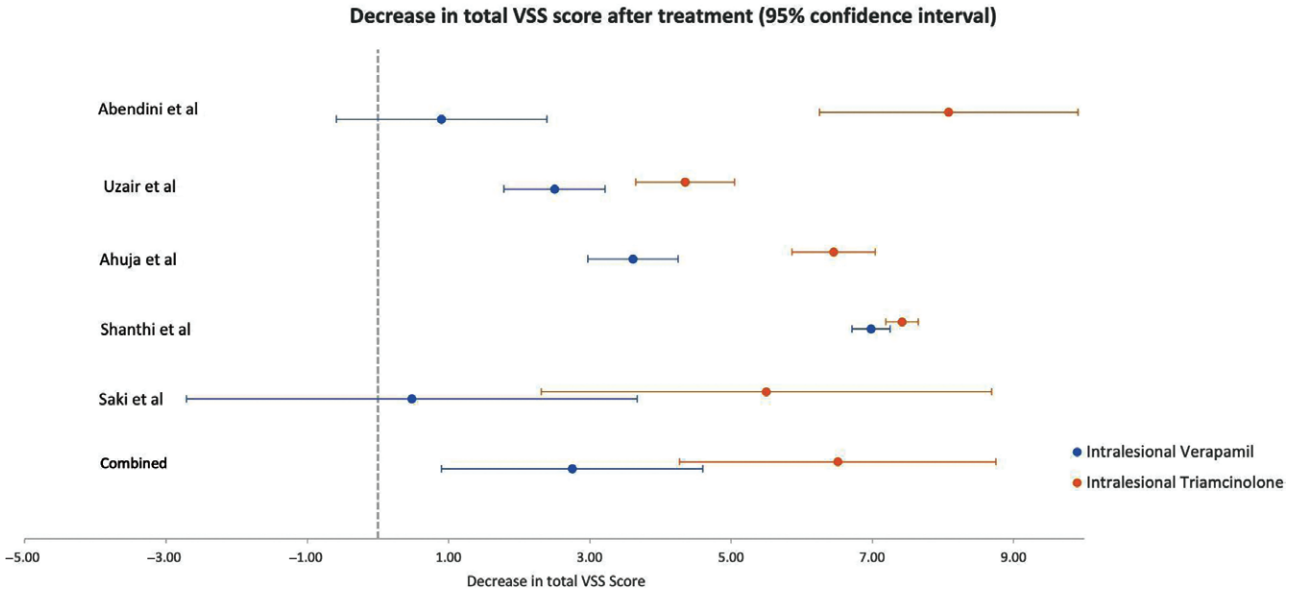

Fig. 4. Plot of decreases in total VSS score per treatment.

triamcinolone acetonide at 43.5%, whereas the rate in the verapamil group was only 6.4%. In Figures 6 and 7, the number of patients who reported each adverse effect per treatment group and study can be better visualized. From these graphics, we can grasp the large difference in the quantity of side effects between the two groups.

LIMITATIONS

This meta-analysis was limited by both study design and amount of studies. Unfortunately, the limited existing studies comparing these treatment modalities have not been performed or reported in a standardized manner, making compilation and pooling of data difficult.

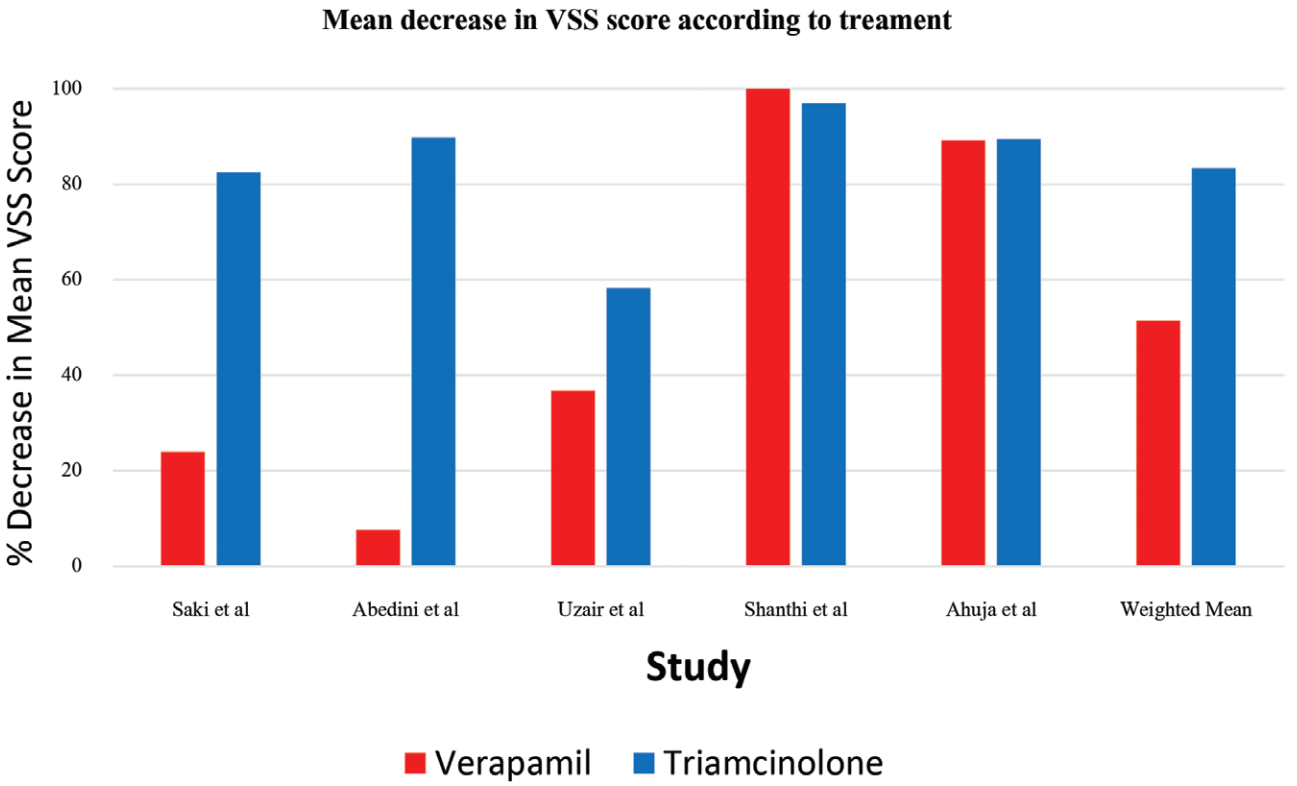

Fig. 5. Mean percent decrease in VSS score per treatment.

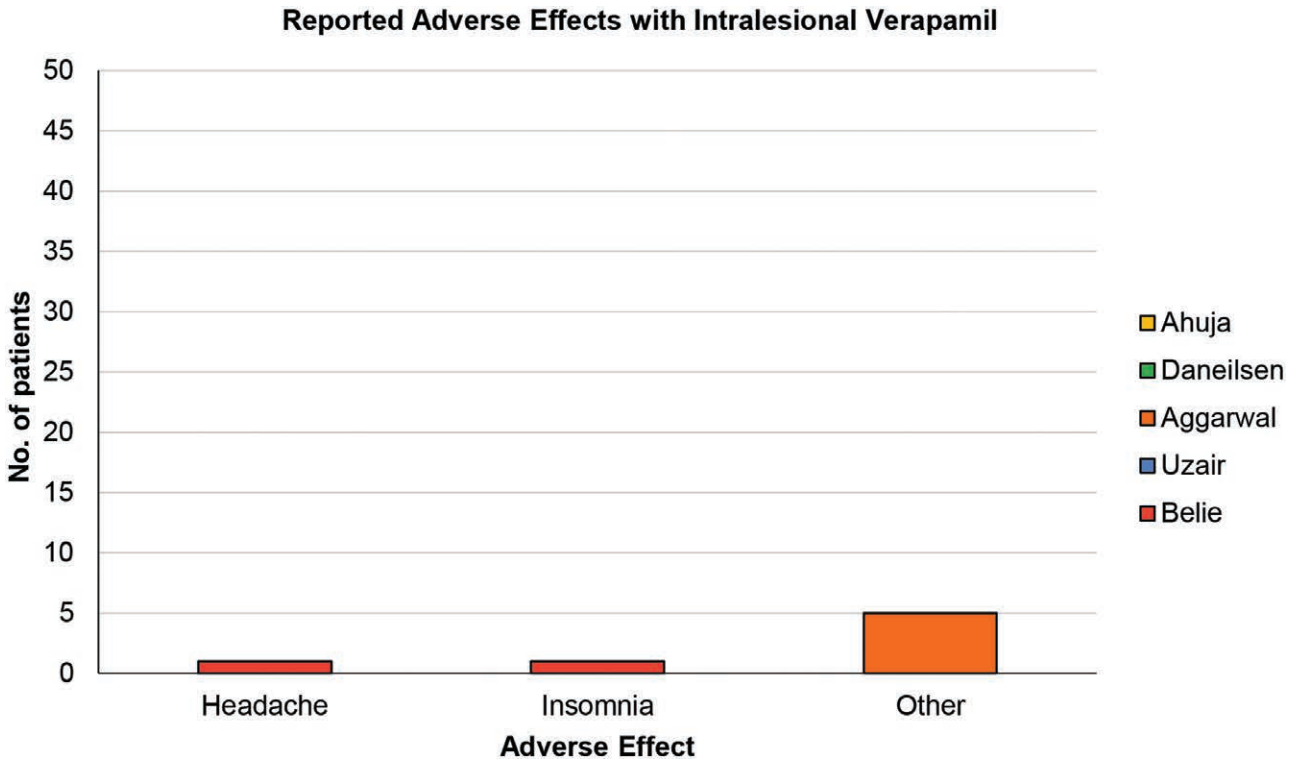

Fig. 6. Reported adverse effects with intralesional triamcinolone.

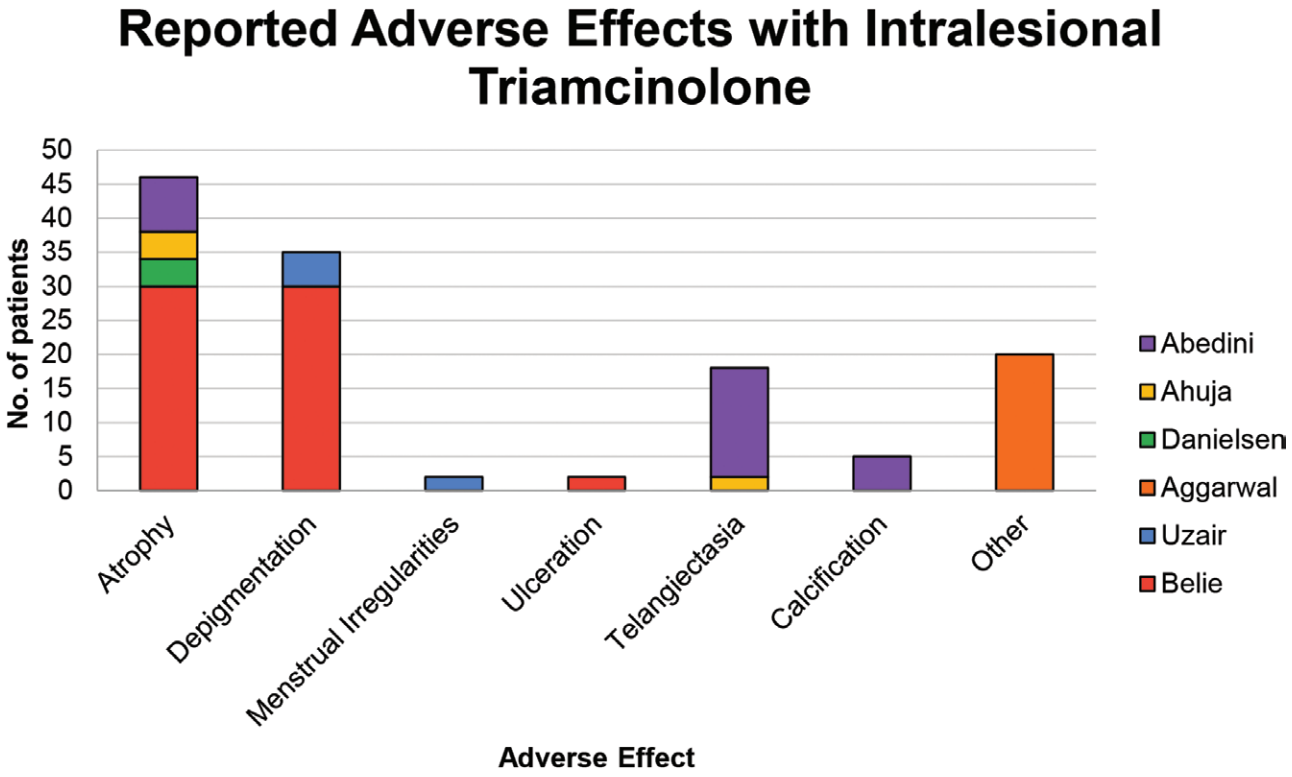

Fig. 7. Reported adverse effects with intralesional verapamil.

Using the GRADE tool[31] to evaluate the certainty of evidence for the included studies, we determined that most included studies were very-low to low/moderate on this scale. Although all the studies were randomized controlled studies, many had small sample sizes and all had a high risk of bias due to the nature of evaluation of keloids. For example, the VSS score itself leaves moderate room for interpretation. Specifically the aspects of grading vascularity and pigmentation are mostly subjective values and therefore rely on consistency of the interpreter. Furthermore, comparing subjective data from different interpreters across many studies greatly opens the risk for bias. However, this risk was unavoidable as the VSS score appears in a vast amount of keloid research and a more standardized scale has yet to be developed.

Verapamil and Triamcinolone Combined

As we can see, there are pros and cons to both of the discussed treatment options as well as very different mechanisms of action. To our knowledge, only one clinical study thus far has investigated the combined effects of verapamil and triamcinolone to allow the patient to get the results of both. Kant et al studied this innovative treatment on 58 patients with either keloid or hypertrophic scars.[10] The etiology of the included scars had a different distribution than what was seen in our meta-analysis. The most common etiology in their study was surgery followed by trauma. This could be due to a difference in participant recruitment methods.

The patients were injected with 0.1–0.2 mL of a 1:1 ratio of triamcinolone acetonide 40 mg/mL and verapamil 2.5 mg/mL. They received three total injections: at 1 week, 2 weeks, and 5 weeks. They were then followed up for up to 24 months. Scars were evaluated with the Patient and Observer Scar Assessment Scale, which has similar components as the VSS, including evaluation of vascularity, pigmentation, and pliability, but it also evaluates thickness, relief, surface area, pain, and pruritus.

They found a statistically significant decrease from the keloid Patient and Observer Scar Assessment Scale baseline scores at follow-up from 3 to 6 months.[10] This included decreases in every component of the score with significant decreases in pain, pruritus, scar relief, pliability, and surface area. They report that all patients who underwent the full treatment regimen had fast improvement of their scars. Furthermore, those patients who followed up for more than 12 months still retained a decrease in baseline Patient and Observer Scar Assessment Scale score showing the ability of combination triamcinolone and verapamil to be effective in the long term.[10]

With the combination treatment of triamcinolone and verapamil injections, very few side effects were noted. Only one patient had hardening of the scar, one had indentation, and there were some reports of pruritis for a short duration. This is a great improvement from the side effects reported with triamcinolone monotherapy, which can potentially allow patients to receive the benefit of the triamcinolone mechanism without the adverse effects.

Additionally, there was one mouse model created to study this combination treatment effect.[11] The authors implanted excised human hypertrophic scars into the backs of mice and treated them in three injection type groups: normal saline, verapamil, and triamcinolone+verapamil. They then analyzed the fibroblast viability, proliferation, and scar weights for 4 weeks. They concluded that combination therapy was able to yield an equal or greater efficacy while being able to decrease the adverse effects seen in monotherapy, which is consistent with the previously described clinical study.[11]

CONCLUSIONS

The best treatment of keloids still remains a point of contention among clinicians. Research has shown multiple treatments that yield promising results and yet no one treatment method has risen to become the golden standard.

When comparing the modalities of triamcinolone and verapamil, better and faster results are seen when using triamcinolone; however, there are also increased adverse effects such as atrophy, skin ulceration, and hypopigmentation. Minimal combination studies of these treatments have shown that perhaps using them together can augment their mechanisms without the unwanted side effects. More trials need to be completed using this method to gain a full understanding of this combination therapy.

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ACKNOWLEDGMENTS

The authors thank the Conrad and Jobst Foundation. The authors would also like to thank Mariam Abouahmed, MPH for her administrative assistance and manuscript submission.

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