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LETTER TO THE EDITOR

Intralesional Triamcinolone Acetonide for Keloid Treatment: A Systematic Review

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Introduction

The keloid lesion is a hypertrophic scar dysfunction with continuous growth and tumoral shape that usually presents with a hyperemic aspect accompanied by pruritus and pain [6, 12]. This disease can have a prevalence reaching 16% in dark-skinned populations. Those who carry the disease will experience psychosocial impairment and loss of quality of life [16].

The physiopathogenesis of keloids is not completely clear in the medical literature, although it has been the focus of many studies, and this has led to empirical treatments with debatable success [7, 15]. One of the most frequently used treatments is intralesional corticotherapy with triamcinolone acetonide, isolated or in association [10].

However, the literature presents no consensus on the ideal drug concentration for injection into the keloidal scar. Therefore, this study aimed to explore the most effective concentration and application periodicity of triamcinolone acetonide for intralesional injections in keloids.

Methods

Study Inclusion Criteria

Studies

Controlled and randomized trials that evaluated the exclusive effectiveness and safety of intralesional corticoid applications for keloid treatment were included in this study.

Subjects

Subjects of any race, gender, or age with a keloid scar in any anatomic region who had not previously received any type of clinical or surgical treatment were included in the study. Clinically active keloid scars of any etiology with any time of progression were included. The keloids were diagnosed by the macroscopic aspect of the lesion and clinical symptoms such as pain, pruritus, and hyperemic aspect.

Interventions

The applications of intralesional triamcinolone acetonide for keloid scars were evaluated, with no restriction as to drug concentration, injection form, or periodicity.

Clinical Outcomes

The reduction in extension and thickness of the keloid scar and in the clinical symptoms of pruritus, pain, and hyperemia were evaluated.

Search Strategy for Identification of Trials

A systematic review of the literature was performed using the Medline, Lilacs, and Web of Science databases as well as the Cochrane Database of Systematic Reviews as of October 29, 2007. A high-sensibility and low-specificity search strategy formulated from keloid and triamcinolone acetonide–related keywords, synonyms, and abbreviations was used for each database (Fig. 1).

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Medline via Pubmed Strategy

(Keloid* OR Acne Keloid OR Acne Keloids OR Keloid, Acne OR Keloids, Acne OR Folliculitis Keloidalis OR Keloidal Acne OR Acne, Keloidal OR Keloidal Acnes OR Acne Keloidalis OR Keloidal) AND (Triamcinolone Acetonide OR Acetonide, Triamcinolone OR Azmacort OR Cinonide OR Kenacort A OR A, Kenacort OR Kenalog OR Kenalog 40 OR 40, Kenalog OR Tricort-40 OR Tricort 40 OR Tricort40 OR Hydroxycorticosteroids OR Glucocorticoids OR Hydrocortisone OR Cortisol OR Cortifair OR Cortril OR Hydrocortisone, (11 alpha)-Isomer OR 11-Epicortisol OR 11 Epicortisol OR Epicortisol OR Hydrocortisone, (9 beta,10 alpha,11 alpha)-Isomer OR Cortisone OR Adreson) AND (Injections, Intralesional OR Intralesional Injections OR Injection, Intralesional OR Intralesional Injection OR Intralesional OR Injections OR Injection OR Intrakeloid OR Intra-keloid OR Intrawound OR Intra-wound OR Intra-keloid injection OR Intrawound injection) AND (randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR random allocation OR double blind method OR single blind method OR clinical trial OR clinical trials OR (clinical* AND trial*) OR single* OR double* OR treble* OR triple* OR placebos OR placebo* OR random* OR research design OR comparative study OR evaluation studies OR follow-up studies OR prospective studies OR control* OR prospectiv* OR volunteer*)

Lilacs via BVS Strategy

("keloid" or "acne keloid" or "keloidal" or "keloidal acne" or "keloidian" or "keloids" or "keloyds") and ("triamcinolone" or "triamcinolone acetonide" or "triamcinoloma" or "triamcinolona" or "triamcinolona acetonida" or "triamcinolone" or "triamcinolone acetonide" or "triancinoloma" or "triancinolona" or "triancinolona acetonida" or "hydroxycorticosteroids" or "hydroxycorticosterone" or "glucocorticoids" or "glucocorticosteroides" or "glucocorticosteroids" or "glucocortidoides" or "glucocortocoids" or "hydrocortisone" or "hydrocrotisone" or "cortisol" or "cortisona" or "cortisone") and ("intralesional" or "intralesionally" or "injections, intralesional" or "injections")

Web of Science via ISI Strategy

(Keloid* OR Acne Keloid OR Acne Keloids OR Keloid, Acne OR Keloids, Acne OR Folliculitis Keloidalis OR Keloidal Acne OR Acne, Keloidal OR Keloidal Acnes OR Acne Keloidalis OR Keloidal) AND (Triamcinolone Acetonide OR Acetonide, Triamcinolone OR Azmacort OR Cinonide OR Kenacort A OR A, Kenacort OR Kenalog OR Kenalog 40 OR 40, Kenalog OR Tricort-40 OR Tricort 40 OR Tricort40 OR Hydroxycorticosteroids OR Glucocorticoids OR Hydrocortisone OR Cortisol OR Cortifair OR Cortril OR 11-Epicortisol OR 11 Epicortisol OR Epicortisol OR Cortisone OR Adreson) AND (Injections, Intralesional OR Intralesional Injections OR Injection, Intralesional OR Intralesional Injection OR Intralesional OR Injections OR Injection OR Intrakeloid OR Intra-keloid OR Intrawound OR Intra-wound OR Intra-keloid injection OR Intrawound injection)

Cochrane Database of Systematic Reviews Strategy

keloid or keloids or (acne and keloid) or (acne and keloids)

Fig. 1 Search strategy applied to the database

The search strategy was carried out according to the recovery patterns stipulated by each database. Study identification was not restricted by the date, language, periodical, or country of origin of the published study.

Standard Methods of Review

Selection of Trials

Using the search strategy, two researchers independently evaluated the identified studies, grouping them into selected and nonselected trials according to data in the titles and abstracts. Debatable studies for which it was not possible to determine the applied methodology by the title or abstract were evaluated by their complete texts and then classified. The articles related to the studies identified and their references also were verified according to the same criteria.

The selected studies were compared between the researchers, and discrepancies were resolved by discussion and consensus. The selected articles then were evaluated in full, independently, according to the stipulated inclusion criteria. The included and excluded articles were compared between the researchers in a new consensus meeting. Finally, to avoid inclusion of the same data published in different

journals, the articles included for review were analyzed using as parameters authorship, coauthorship, and research sites.

Quality of Evaluation

Two researchers independently evaluated the methodologic quality of the included studies according to the suitability of the subject randomization method. This evaluation classified the studies into categories that varied from A to D and were closely related to the description of subject randomization (Fig. 2). Only studies included in categories A and B were included.

As a supplement to this method, the Jadad study quality scale was applied to all the studies included [8]. Any discrepancy of opinion between researchers was resolved after discussion and consensus.

Data Extraction

Results data from studies pertinent to clinical outcome analysis were extracted independently by two separate researchers. A standardized form based on information required by the clinical outcomes evaluated was used. When necessary, authors of the primary studies were contacted for additional information or data on their study results.

Statistical Analysis

Descriptive Analysis

The variables considered qualitative on the nominal scale were keloid regression, pruritus, pain, and hyperemia. An assessment of external and internal validity was planned for each study, together with a grouping of the studies according to their methodologic and statistical homogeneity for metaanalysis calculations.

Inferential Analysis

Comparisons of the estimated effects among the interventions were calculated using the Review Manager (RevMan 4.2.8, software created by Cochrane Library) program. A p value less than 0.05 was considered the significance level for rejection of the null hypothesis. Results were expressed as relative risk with a 95% confidence interval, and graphics were constructed in a randomized fashion. When necessary, sensitivity tests were applied to subgroup analyses and estimates of the global effect.

Results

The articles identified included 2 from the Medline database, 2 from the Lilacs database, 45 from the Web of Science database, and 12 from the Cochrane Systematic Reviews Database. Of these, 10 were complete systematic reviews and 2 were review protocols. A total of 61 articles were identified.

Seven different research designs were retrieved (systematic reviews and review protocols are the same as research designs). The three controlled and randomized clinical trials identified were focused on the effectiveness of injectable triamcinolone acetonide versus other treatments, and not on different concentrations of the drug. Although 12 systematic reviews and 2 review protocols were retrieved, none of the studies investigated the objective proposed by this study (i.e., to explore the most effective concentration and application frequency of triamcinolone acetonide for intralesional injection in the keloid) (Fig. 3).

Discussion

No effective treatment for keloids exists that can guarantee a definitive cure [7, 8]. The currently proposed interventions intend to prevent recurrence of the keloid scar but do not, in fact, affect its genesis [1, 9].

Applied intralesionally, triamcinolone acetonide is one of the most widely used treatments for keloids, whether alone or in combination with another type of treatment [17]. Keloid involution, represented by attenuation of

Categories	Description
A	Allocation concealment adequate and described in the methodology of the study.
B	Allocation concealment mentioned, but not described in the methodology of the study.
C	Inadequate allocation concealment.
D	Non-Randomized Study

Fig. 2 Classification of the studies

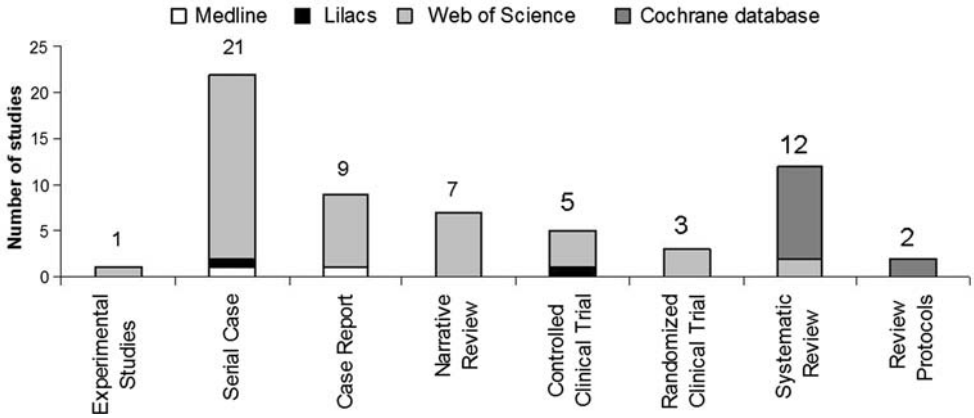

Fig. 3 Number of articles found in each database researched

symptoms including pruritus, pain, hyperemic aspect, and thickening, seems to occur by mechanisms related to a decrease in synthesis, an increase of collagen disintegration, or both [2, 5, 12].

Intralesional injection of triamcinolone acetonide causes a drop in collagen synthesis, which could be a result of fibroblast hypoactivity, a reduction in fibroblast density, or even a maturation modification of these cells. Additionally, it has been noted that this corticosteroid provokes a decrease in new endothelial buds from blood vessels [13, 14].

In reference to the increased collagen disintegration, triamcinolone acetonide seems to cause a significant plunge in alpha-1-antitrypsin and alpha-2-macroglobulin levels, which tend to be greater in keloidal tissue and are natural inhibitors of collagenase in human skin [3,4]. Nevertheless, no defined protocol exists that specifies the appropriate concentration and application mode for this drug. In the face of this gap, the current systematic literature review was proposed.

A controlled and randomized clinical trial is the primary study that provides the best level of evidence for therapeutic interventions [14]. On the other hand, quasi-randomized studies have an inappropriate randomization method, so their results furnish inferences subjected to a greater number of biases, as do those retrospective studies as well [14]. Hence, to warrant possible generalization of the results from this study, it was stipulated that only the controlled and randomized clinical trials would be included. Intervention-blinding methods, although possible and ethical for injections of different triamcinolone acetonide concentrations into the keloid, were not considered a criterion for inclusion of trials, but rather a condition to be taken into consideration in assessing methodologic quality.

The subject inclusion criteria and keloid lesions adopted in this study reflect a prior expectation that primary studies evaluating the proposed intervention would be lacking [14]. The only criterion for subject exclusion was the absence of any previous treatment for the keloid. This condition was stipulated to avoid a possible bias by synergism of different treatments applied to the same keloid. With the same intention, concentrations of triamcinolone acetonide and forms of intralesional injection also were not restricted.

For analysis of the results, the clinical outcomes evaluated were considered possible variables of the nominal categorical scale. This criterion was adopted to increase the probability of identifying primary studies and attenuating possible statistical heterogeneity of inferential analysis, even if the fine analysis of results was hindered. However, no studies were identified that fit the inclusion criteria.

Nonetheless, the concentration and fractioning of triamcinolone acetonide proposed by Ketchum et al. [11] and based on clinical practice have been divulged since the 1970s. The absence of randomized clinical trials reinforces the empirical characteristic of treating keloids with triamcinolone acetonide. Consequently, there is an urgent need for controlled and randomized trials, especially considering the prevalence of keloids in both plastic and general surgery, to determine a standardized protocol for intralesional treatment of keloids with triamcinolone acetonide.

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