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Randomized Double-Blind Clinical Trial Comparing Clobetasol and Dexamethasone for the Topical Treatment of Symptomatic Oral Chronic Graft-Versus-Host Disease

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A B S T R A C T

Patients who undergo allogeneic stem cell transplantation frequently develop an immunologic disease caused by the reactivation of the graft to the host tissues. This disease is called graft-versus-host disease (GVHD) and it is usually a systemic disorder. In a large proportion of cases, oral disorders that are related to a chronic phase of GVHD (cGVHD) occur, and their treatment involves the use of topical immunosuppressive drugs. Several medications have been studied for this purpose, but only a small number of clinical trials have been published. The present study is a randomized, double-blind clinical trial that compares topical clobetasol and dexamethasone for the treatment of symptomatic oral cGVHD. Patients were randomly assigned to treatment with clobetasol propionate .05% or dexamethasone .1 mg/mL for 28 days. In both arms, nystatin 100,000 IU/mL was administered with the corticosteroid. Oral lesions were evaluated by the modified oral mucositis rating scale (mOMRS) and symptoms were registered using a visual analogue scale. Thirty-five patients were recruited, and 32 patients were randomized into the study groups: 18 patients (56.3%) to the dexamethasone group and 14 patients (43.8%) to the clobetasol group. The use of clobetasol resulted in a significant reduction in mOMRS total score ($P = .04$) and in the score for ulcers ($P = .03$). In both groups, there was significant symptomatic improvement but the response was significantly greater in the clobetasol group ($P = .02$). In conclusion, clobetasol was significantly more effective than dexamethasone for the amelioration of symptoms and clinical aspects of oral lesions in cGVHD.

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is an important late complication in allogeneic hematopoietic stem cell transplant (HSCT) recipients [1]. In this setting, oral cavity involvement with cGVHD is frequent, with an estimated prevalence of 80% to 100% of cases [2,3]. Oral cGVHD lesions have clinical and pathological characteristics very similar to those of oral lichen planus (OLP) [3-5]. According to the National Institutes of Health (NIH) consensus criteria for cGVHD [1], the clinical oral manifestations of cGVHD include lichenoid lesions, pseudomembrane ulceration, atrophy, erythema, and mucoceles. The criteria also consider symptoms, including oral sensitivity, pain, taste disturbances, and dry mouth [6,7]. Oral lesions of chronic GVHD are commonly refractory to immunosuppressive systemic therapy; therefore, the addition of topical agents to systemic therapy is frequently necessary [2,8,9]. Despite this knowledge, there is no defined recommendation for the topical treatment of cGVHD oral lesions.

Several medications have been studied for the topical treatment of these lesions, such as azathioprine, tacrolimus, dexamethasone, and budesonide [10-19]. These studies have shown that topical treatment results in improvement of the clinical or symptomatic aspects of the oral lesions; however, these were case reports or series of cases. The results of previous clinical trials have shown that topical treatment improves the clinical aspects of the lesions and provides better results than systemic treatment alone [13,19,20].

The present study was a randomized, double-blind clinical trial comparing 2 topically administered corticosteroids (clobetasol versus dexamethasone) for symptomatic cGVHD oral lesions. As clobetasol has been shown to have greater potency than dexamethasone [21,22], we hypothesized that clobetasol would provide a better response than dexamethasone.

MATERIALS AND METHODS

This study was designed as a randomized, double-blind clinical trial. Patients were recruited from the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro and from the Hematology and Hemotherapy Center of the Campinas University (Hemocentro/Unicamp) from October 2008 to May 2012. Patients with oral lesions of cGVHD were asked if they presented sensitivity on the oral mucosa. All the patients who presented symptomatic oral lesions of cGVHD were invited to participate in the study. They were informed of the aims, risks, and benefits of the study and signed a consent form. Patients who fulfilled the inclusion criteria were

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identified by the medical staff and referred for a dental appointment. Patients with a history of allergy to the tested medications, as well as those under topical treatment for oral lesions of cGVHD in the last 3 months, were excluded from the study. Systemic immunosuppressive treatments were not considered as an exclusion criteria. This research was approved by the review boards of both institutions and was registered in ClinicalTrials.gov under the identifier NCT01699412.

Because there are few clinical trials on oral cGVHD, the sample size of the present study was calculated based on studies of OLP. The expected symptomatic improvement was 100% for the clobetasol group and 38.5% for the dexamethasone group [23,24]. Using a significance of 95% and power of 80%, the sample size was calculated as 30 patients with 15 patients in each study group. Accounting for an expected loss of 20% from protocol inclusion and randomization, we aimed to enroll 38 patients.

Randomization

Patients included in the study were randomly assigned to 1 of 2 study groups using Random Allocation Software 1.0 (Isfahan University of Medical Sciences, Isfahan, Iran). Randomization was performed at a central location.

One group rinsed their mouths with 5 mL of a solution of clobetasol propionate .05% administered with nystatin 100,000 IU/mL and the other group rinsed with 5 mL of a solution of dexamethasone .1 mg/mL administered with nystatin 100,000 IU/mL. Patients were instructed to use the solution for 1 minute timed by a clock, 3 times a day, for 28 days.

Both medications were prepared centrally at the School of Pharmacy of Federal University of Rio de Janeiro. Both solutions had similar taste, color, and smell; labels were numbered and did not identify the medication.

Data Collection

Clinical and demographic characteristics of the patients were obtained from medical records. Clinical evaluations were performed at baseline and after 28 days of treatment using symptomatic and morphologic criteria. Symptoms (oral sensitivity, pain, and xerostomia) were recorded by the patients using a visual analogue scale (VAS) [4,25,26]. Patients were evaluated by an oral medicine expert who was familiar with the evaluation of oral cGVHD lesions. Oral lesions of cGVHD were diagnosed according to the NIH consensus criteria for cGVHD and graded by the modified Oral Mucositis Rating Scale (mOMRS) [1,27]. Biopsy was performed in cases in which cGVHD had not been previously established. Adherence to treatment and adverse effects were analyzed at the end of the treatment, through a questionnaire.

Primary Outcome

The primary study outcome was the improvement of symptoms. Patients were asked to mark in a VAS how much sensitivity they presented on the oral mucosa. Oral sensitivity was considered when the patient reported symptoms greater than 0 on the VAS. Symptomatic improvement was defined as the range between the VAS before and after therapy. The improvement was categorized as (1) total remission, ie, reduction in the VAS to 0; (2) partial remission, ie, reduction of at least 2 cm in VAS; and (3) no remission, ie, changes not greater than 2 cm in VAS. Patients who presented VAS at baseline lower than 2 cm, and who showed reduction to 0 on VAS at the end of the treatment, were considered as total remission. Median reductions in the differences in the VAS scores were compared between the study groups (VAS at baseline less VAS at the end of the topical treatment).

Secondary Outcomes

Morphologic improvement was considered as a secondary outcome and was defined as the total reduction in mOMRS total score throughout the study (mOMRS total score at baseline less mOMRS total score at the end of the topical treatment). Additionally, the median reductions in the mOMRS scores for erythema, lichen-type hyperkeratosis, ulcers, and mucoceles were compared between the study groups.

Additionally, oral dryness was evaluated by the presence of xerostomia and by measuring salivary flow rates (SFR). Patients were asked to mark in a VAS how much dryness they presented in the mouth. To analyze the cases of persistent daily dry mouth, xerostomia was considered only when scored as $\geq$ 2 cm on VAS. The median VAS scores for xerostomia at baseline and at the end of the topical treatment were compared between the study groups. Resting saliva samples were collected under standard conditions, after the oral evaluation [28,29]. Reduced SFR was considered when measured as $<$ .3 mL/minute [30]. The median resting SFR at baseline and at the end of the topical treatment were compared between the study groups.

Statistical Analysis

All statistical analysis was performed using SPSS for Windows software (version 17.0, IBM, Chicago, IL). The chi-square test or Fisher exact test was used to compare proportions, and the Mann-Whitney and Wilcoxon tests were used to compare continuous variables. *P* values $<$ .05 were considered statistically significant.

RESULTS

A total of 35 patients were recruited for the study. Three patients were excluded (2 patients were under topical treatment for oral cGVHD, 1 patient declined to participate in the study). Thirty-two patients were randomized into the study groups: 18 patients (56%) to the dexamethasone group and 14 patients (44%) to the clobetasol group (Figure 1).

Clinical and demographic data on the 32 studied patients are summarized in Table 1. Most patients had GVHD classified as overlap syndrome (66.7%) and were receiving some systemic treatment for GVHD (62.5%). The first study evaluation was performed at a median of 471 days (range, 83 to 2405 days) after the HSCT. The most commonly affected organs were skin (56%), liver (47%), and eye (44%). The observed oral manifestations of cGVHD at baseline are presented in Table 2. On baseline exam, erythema and atrophy were present in 91% and 81% of patients, respectively. Ulcers,

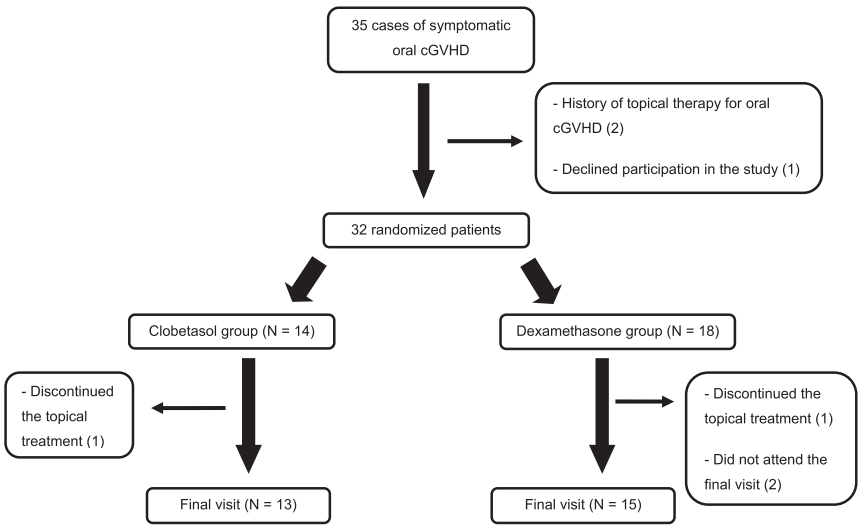

Figure 1. Flow chart of patients throughout the study.

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