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TOPICAL ADMINISTRATION OF TACROLIMUS AND SYSTEMIC CORTICOSTEROIDS IN TREATMENT OF ORAL AND NASAL MUCOUS MEMBRANE PEMPHIGOID IN A SAMPLE OF EGYPTIAN POPULATION: A RANDOMIZED CONTROL TRIAL

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ABSTRACT

Objectives: The study aimed to evaluate the effect of topical tacrolimus as adjunctive to systemic corticosteroids in treatment of mucous membrane pemphigoid.

Material & Methods: The present study was conducted on 76 patients with severe mucous membrane pemphigoid according to chan et al classification. Patients were allocated (1:1) to a group. Group A (control group) patients treated with 40 mg systemic corticosteroids alone and group B (Study group) patients were treated with 40 mg systemic corticosteroids and topical tacrolimus as adjunctive to corticosteroids. Total ulcers score (site, activity, and pain score) was recorded in both groups on weekly basis till the full recovery of oral, oropharyngeal and nasal lesions.

Results: Both treatment regimen had shown a significant improvement in total ulcer scores with ($P<0.001$) of the oral and nasal lesion scores from the beginning of the study to its end, but the study group (combination of corticosteroids and tacrolimus) revealed significant decrease ($P<0.001$) compared to the study (corticosteroid alone) group.

Conclusion: The use of topical tacrolimus as adjunctive to systemic corticosteroids could improve healing and total ulcer score in severe cases of mucous membrane pemphigoid than solo treatment with systemic corticosteroids

KEY WORDS: Mucous membrane pemphigoid, Systemic corticosteroids, Topical tacrolimus, Total ulcers score.

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INTRODUCTION

Mucous membrane pemphigoid (MMP) is one of the autoimmune mucocutaneous disorders which is characterized by the appearance of multiple blisters on the different mucous membranes and skin [1]. It was estimated that the incidence of MMP is 1.3–2.0 per one million people per year and its treatment can be difficult and often disappointing to the patients and usually affects patients' quality of life [2].

Pathogenesis of MMP is complex; however, it may be explained by the production of autoantibodies which are directed to several basal membrane components, such as collagen VII and XVII, laminin 5 and a6/b4 integrin. This combination is followed by formation of sub-epidermal blisters [3,4].

Management of MMP requires a multidisciplinary approach aiming to improve symptomatology, interrupt disease progression and prevent chronic inflammatory process sequelae and tissue scarring [5].

The outcome of MMP treatment depends on the involved areas as well as early treatment. Involvement of the oral mucosa alone is considered to be of lower risk, while involvement of ocular, esophageal, nasal, genital and laryngopharyngeal mucosa is usually associated with irreversible scarring. Topical treatment with corticosteroids is considered to be the gold standard for therapy of MMP. For the low-risk patients, potent topical corticosteroids in combination with systemic dapsone or tetracycline might be sufficient. [3,6]

However, in refractory or high-risk oral corticosteroids in combination with azathioprine, or mycophenolic acid should be considered. Other therapeutic option includes intravenous treatment with cyclophosphamide, immunoglobulins, or rituximab represents in severe treatment-resistant cases [6].

On the other hand, topical steroids showed a limited role in management of MMP and may be used just to control gingival desquamation. Therefore, prednisolone (1–2 mg/kg/day) is considered to be the first line of treatment and is usually followed by gradual tapering and combining immunosuppressants. If a dose above 100 mg/day is required, pulsed intravenous corticosteroids are recommended [7,8].

Topical tacrolimus ointment reported to provide successful therapy not only in the oral cavity, but also in patients with mucosal involvement [10,11]. It is recommended to apply topical tacrolimus twice daily, according to patient tolerance [5, 11].

Tacrolimus acts as a topical immunosuppressant as it inhibits and decreases the release of several pro-inflammatory cytokines [5].

The present study focused the light on the effect of tacrolimus as adjunctive to systemic steroid in management of MMP in a sample of Egyptian patients.

MATERIALS AND METHODS

Type of study: A Randomized controlled clinical trial

Sample size: A power analysis was designed to have adequate power to apply a two-sided statistical test of the null hypothesis that there is no difference would be found between different groups. By adopting an alpha level of (0.05) a beta of (0.2) i.e. power=80% and a critical z value of (1.96) calculated based on the results of a previous study [12], the predicted sample size (n) was a total of (62) cases (31 cases per group). Sample size was increased by 20 % to compensate for possible dropouts during follow-up intervals to be (76) cases (i.e 38 cases per group). Sample size calculation was performed using G*Power version 3.1.9.7.

Subjects: 76 participants, 30 males and 46 females aged from 32 to 63 were recruited from outpatients' clinic ENT of Rayan hospital and diagnosis clinic of faculty of dentistry Cairo university. All the participants were diagnosed with severe mucous membrane pemphigoid that is manifested clinically by presence of oral lesions with other lesions that may affect eyes, nasopharynx, larynx, genital organs according to chan et al. [13] Oral lesions are manifested as tense blisters with mucosal erosion. [14]

The diagnosis was confirmed by detection of linear deposition of both IgG and C3 on epithelial basement membrane zone (BMZ) by direct immunofluorescence. [1,3,14] Patients were selected according to inclusion and exclusion criteria.

Inclusion criteria

Patients whose able and will attend all the prescheduled visits designed for the study, patients with severe mucous membrane pemphigoid according to Chan et al classification [13] with oral manifestations and with or without nasal manifestations. No medical history with other immunosuppressive drugs three months prior to the study and no medical history with oral or topical corticosteroids for at least one month.

Exclusion criteria

Absence of contraindication to both corticosteroids and tacrolimus therapy including uncontrolled diabetes mellitus patients, pregnant women, hypertensive and osteoporotic patients.

After patients' selection according to the inclusion and exclusion criteria and the confirmation of their diagnosis clinically and immunohistochemically, all the participant's demographic data were recorded and then participants were randomly allocated by using computerized generated table to one of both groups. Group A (control group) patients treated with systemic corticosteroids alone and group B (Study group) patients were treated with systemic corticosteroids and topical tacrolimus as adjunctive to corticosteroids.

After patients' selection according to inclusion and exclusion criteria, they were randomly and equally allocated by using a computerized generated table into one of the two groups; Group A (control group) where systemic corticosteroids were administrated alone, and group B (study group) where topical tacrolimus were administrated as adjunctive to systemic corticosteroids, 40mg Systemic corticosteroids (prednisone) were administrated to all the participants in both groups with monitoring its side effects till the patients achieve clinical remission, then gradual withdrawal of corticosteroids was applied. Topical antifungals were administrated for a week for each month to avoid candida infection, while topical 0.03% tacrolimus ointment (Protopic) were administrated in group B (study group) as adjunctive to 40 mg systemic corticosteroids. Topical tacrolimus was applied on mucosal lesions as the patients were instructed to dry the area of application and then apply a thin layer and not to eat for an hour after ointment application [15] and applied to nose and nasopharynx by using a tacrolimus ointment in a syringe with a applicator after training patients how to use the applicator twice daily and follow up and healing assessment were done under endoscopic vision day after day from the beginning of the treatment till clinical remission detected, then application of tacrolimus was applied once till the complete remission of lesions (Fig A,B,C,D) .[5]

A weekly follow up visits were designed for all the patients to assess remission state, ulcers total score was recorded at the beginning of the study, at each follow up visits to assess the effect of systemic corticosteroids and systemic corticosteroids with topical tacrolimus treatment on the duration of remission of mucosal lesions and its effect on ulcers healing (Table 1)

Methods of assessing ulcers total score

Ulcers total score were assessed and recorded according to table (1) [16].

Site score is recorded as 0 if there is no lesion and as one if lesion is present. For the buccal mucosa if less than 50% of area is affected then it is recorded as 1, if more than 50% of area is affected then it is recorded as two. For dorsum of tongue, floor of mouth, hard, soft palate, and oropharynx, if lesion is unilateral then it is recorded as one, if the lesion bilateral it is recorded as two. Activity score is recorded as one for mild erythema, two for marked erythema without erosion and three for erosion or ulceration. Analogue pain score was used to assess pain score, where no discomfort recorded as zero and gradual increase till it reaches 10 that represents the most severe pain. [16]

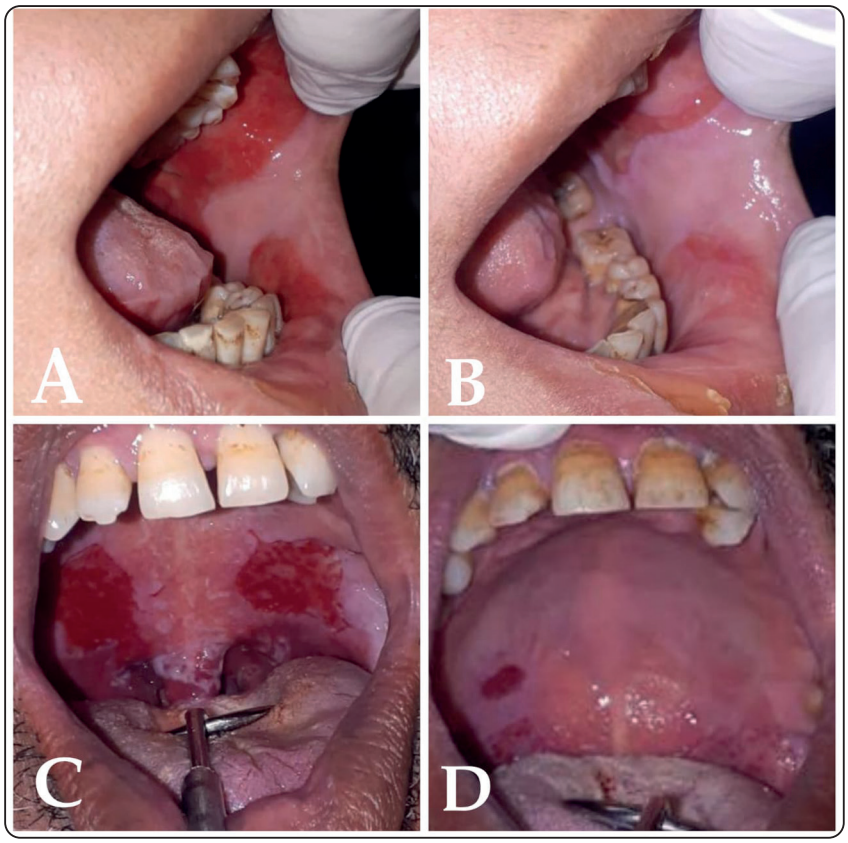

Fig. (1) Photographs of (A) represent severe erosions and ulcerations in buccal mucosa in mucous membrane pemphigoid control group patients before treatment, (B) represent healing of erosion and ulcerations in buccal mucosa in mucous membrane pemphigoid control group after treatment with corticosteroids alone, (C) represent severe erosions and ulcerations in palate in mucous membrane pemphigoid study group patients before treatment, (B) represent healing of erosion and ulcerations in palate in mucous membrane pemphigoid study group after treatment with corticosteroids and tacrolimus

TABLE (1): Ulcers total score assessment

Site	**Site score**	**Activity score/ unit of sire (0-3)**
Outer lip (1)		
Inner lip (1)		
R Buccal mucosa (1 or 2)		
L Buccal mucosa (1 or 2)		
Gingivae (1 each segment)		
Lower R (from 1st premolar)		
Lower central (canine to canine)		
Lower L (from 1st premolar)		
Upper R (from 1st premolar)		
upper central (canine to canine)		
Upper L (from 1st premolar)		
Dorsum of tongue (1 or 2)		
R Ventral tongue (1)		
L Ventral tongue (1)		
Floor of mouth (1 or 2)		
Hard palate (1 or 2)		
Soft palate (1 or 2)		
Oropharynx (1 or 2)		
Total		

Total Score= Site Score + Activity Score + Pain score (1-10) (Maximum 106)

RESULTS

The study was conducted on 76 cases that were equally and randomly allocated to each of the studied groups (i.e. 38 cases each). There was no significant difference between both groups regarding sex (p=0.815), age (p=0.725) and site of the lesion (p=1). Demographic data and baseline characteristics are presented in table (2).

Results of inter and intragroup comparisons of oral lesion scores presented in table (3), showed that at baseline, group (B) had significantly higher value than group (A) (p=0.040). While for other intervals, group (A) had significantly higher values (p<0.001).

For both groups, there was a significant difference between values measured at different intervals (p<0.001). Post hoc pairwise comparisons showed values measured at baseline and after 1 week to be significantly higher than other intervals (p<0.001). In addition, they showed values measured after 2 and 3 weeks to be significantly higher than value measured after 4 weeks (p<0.001).

Results of inter and intragroup comparisons of nasal lesion scores presented in table (4), showed that after 1, 2 and 3 weeks, group (A) had significantly higher values than group (B) (p<0.05). For other intervals, the difference was not statistically significant (p>0.05).

For both groups, there was a significant difference between values measured at different intervals (p<0.001). For group (A), post hoc pairwise comparisons showed baseline value to be significantly higher than other intervals except for 1 week (p<0.001). In addition, they showed value measured after 1 week to be significantly higher than values measured after 3 and 4 weeks (p<0.001). Finally, they showed value measured after 2 weeks to be significantly higher than 4 weeks value (p<0.001). For group (B), post hoc pairwise comparisons showed baseline and 1-week values to be significantly higher than other intervals (p<0.001).

TABLE (2): Intergroup comparisons of demographic data and baseline characteristics

Parameter			Group (A)	Group (B)	Statistic	p-value
Sex	***Male***	**n**	15	13	**0.05**	**0.815**
		%	37.5%	32.5%		
	Female	**n**	25	27		
		%	62.5%	67.5%		
Age (years)	***Mean±SD***		47.50±8.83	46.00±9.93	**0.36**	**0.725**
Lesion site	***Oral and nasal***	**n**	65	65	**0.00**	**1**
		%	32.5%	32.5%		
	Oral only	**n**	135	135		
		%	67.5%	67.5%		

TABLE (3): Intergroup comparisons of oral lesions score

Interval	Oral lesion scores (Mean±SD)		Statistic	p-value
	Group (A)	*Group (B)*		
Baseline	56.70±7.55^{A}	61.20±9.38^{A}	**1012.00**	**0.040***
1 week	48.74±6.45^{A}	39.38±9.33^{A}	**1203.00**	**<0.001***
2 weeks	37.84±6.42^{B}	21.53±7.16^{B}	**1378.50**	**<0.001***
3 weeks	28.45±7.33^{B}	11.53±5.77^{B}	**1406.50**	**<0.001***
4 weeks	19.18±6.80^{C}	5.74±2.16^{C}	**1430.00**	**<0.001***
Statistic	**151.62**	**148.12**		
p-value	**<0.001***	**<0.001***		

Different superscript letters indicate a statistically significant difference within the same vertical column; *significant (p<0.05)

TABLE (4): Intergroup comparisons of nasal lesions scores

Interval	Nasal lesion scores (Mean±SD)		Statistic	p-value
	Group (A)	*Group (B)*		
Baseline	4.00±0.00^{A}	3.83±0.39^{A}	**175.50**	**0.123**
1 week	3.00±0.00^{AB}	2.30±0.56^{A}	**247.00**	**<0.001***
2 weeks	2.00±0.00^{BC}	0.83±0.94^{B}	**247.00**	**<0.001***
3 weeks	1.08±0.28^{CD}	0.57±0.51^{B}	**221.00**	**0.004***
4 weeks	0.08±0.28^{D}	0.00±0.00^{B}	**161.00**	**0.203**
Statistic	**51.82**	**82.79**		
p-value	**<0.001***	**<0.001***		

Different superscript letters indicate a statistically significant difference within the same vertical column; *significant (p<0.05)

DISCUSSION

Mucous membrane pemphigoid (MMP) is a rare autoimmune subepidermal blistering disorder characterized by predominant involvement of the external mucosal surfaces with significant variation in clinical presentations with a propensity to affect the mucous membranes more often than the skin. Ultimately, scarring of the mucous membranes occurs, which can result in blindness as well as stenosis of the nasopharynx, trachea, esophagus, vagina, urethra, and rectal mucosa that will affect the patient's quality of life as well as the treatment can be difficult and often disappointing to the patients. [17]

Recently, additional new medication strategies have been reported to be successful in the treatment of MMP as adjunctive to corticosteroids, as tetracycline hydrochloride, niacinamide, topical cyclosporine, Rituximab and topical tacrolimus, in treatment of moderate to severe cases of MMP to improve recovery outcome. [18] This study focused on the effectiveness of adding topical tacrolimus to the well-documented therapy of corticosteroids in controlling severe cases of oral MMP. Tacrolimus is an immunosuppressant macrolide antibiotic that bounds to intracellular protein FKBP-12 through complex formation with calcium, calcineurin, and calmodulin that inhibit the phosphatase activity of calcineurin. By inhibiting calcineurin, Tacrolimus acts on CD4+ T cells to stop the synthesis of IL-2 and stop the recruitment of eosinophils, which is a crucial phase in the pathophysiology of the disease. Tacrolimus also acts on mast cells by preventing histamine release and prostaglandin synthesis. [19] Topical tacrolimus has been successfully used in the treatment of several conditions such as oral lichen planus, oral graft versus host disease and pemphigus vulgaris. Furthermore, tacrolimus is well tolerated when used topically to oral MMP and effectively reduces MMP that does not respond to corticosteroid therapy (6,10). Previous papers reported fewer adverse events when tacrolimus applied topically on different oral lesions as burning, erythema and pruritis. [20,21] but neither of them reported in this study may be due to short duration of application of tacrolimus.

In this study, both treatment regimens resulted in a significant reduction (P<0.001) of the oral and nasal lesion scores from the beginning of the

study to its end, representing the effectiveness of both treatment regimens in treating oral MMP. This finding is also consistent with other that reported a significant decrease in both study groups treated with tacrolimus versus corticosteroid, [22]

The comparison of the two study groups revealed a significant decrease (P<0.001) in the tacrolimus group compared to the corticosteroid group, which was consistent with Barros et al findings. [5] These findings may be due to the effect of tacrolimus on CD4+ T and inhibition of IL-2 synthesis with the stoppage of eosinophils recruitment, and their pivotal role in pathophysiology of the disease. [19]

However, Nazemi-Tabrizi et al. [22] have shown a non-significant reduction of MMP oral lesions between using topical tacrolimus and topical corticosteroids in each group, which in contrast with this study's findings, that indicated a significant reduction of MMP oral lesions in patients who received a combination of tacrolimus and corticosteroids. The difference between the two studies can be attributed to the small number of patients who were included in the Nazemi et al study and the different routes of administration of corticosteroid regimen. Hence, topical tacrolimus in combination with systemic corticosteroids can be a safe and effective treatment for oral MMP, minimizing the negative consequences and problems of systemic immunosuppression, especially in elderly patients.

According to our results, 0.03% topical tacrolimus ointment in conjunction with a low dose of systemic corticosteroid is an effective treatment for oral MMP. The use of topical tacrolimus can decrease the use of corticosteroid dosage and their adverse events. Dentists and Clinicians may find the treatment regimen investigated in this study to be a beneficial therapeutic regimen for oral MMP. To the best of our knowledge, this is the first randomized controlled clinical trial to demonstrate the effectiveness of tacrolimus and corticosteroid combination in the treatment of oral MMP. Randomized control trials are warranted to further investigate the safety and efficacy of topical tacrolimus and corticosteroid combination on a large patient population and long follow- ups.

CONCLUSION

The results suggest that the use of 0.03% topical tacrolimus ointment as adjunctive to systemic corticosteroids in treatment of severe cases of mucous membrane pemphigoid could improve total ulcer score and thus improve patients' quality of life

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