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A Randomized Double Blind Controlled Trial to Compare Metronidazole with Doxycycline for the Treatment of Oral Lichen Planus

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The aim of this study was to compare the efficacy of metronidazole with doxycycline in treatment of oral lichen planus. A double blind clinical trial was performed on twenty patients with asymptomatic oral lichen planus, confirmed by biopsy. After initial examination, patients were randomly assigned to receive 250 mg metronidazole or 100 mg doxycycline twice daily for 4 weeks. Target lesions were assessed at weeks 0, 2, 4 by grid measurement. Complete blood examination and liver function tests were done at fourth week. At the end of the trial, in the doxycycline group one (10%) patient showed partial remission and nine (90%) patients showed no response. In the metronidazole group one (10%) patient showed partial remission and one (10%) patient showed completed remission. Eight (80%) patients were unresponsive to metronidazole. No side-effects were reported from the subjects and there were no significant changes in complete blood examination and liver function test after four weeks of treatment in either group. Results of present study suggest that these drugs are not much effective in treatment of oral lichen planus and statistically significant difference was not seen between the two groups in respect to response to therapy at the end of treatment period ($p>0.05$, $p = 0.503$).

Key words: Oral lichen planus, metronidazole, doxycycline

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INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory condition affecting 1-5% of the general population (Dissemond, 2004). The exact cause of OLP has not been disclosed clearly. However, some etiologic and predisposing factors such as hormonal changes, immunologic problems, genetics and infections are suggested. A delayed hypersensitivity immune reaction, in which the release of cytokines by activated T cells leads to the attraction of inflammatory cells and to the destruction of keratinocytes by cell-mediated cytotoxicity, has been implicated in the pathogenesis of disease (Middel *et al*., 2000). Its response to some antibiotics has been shown by several investigators, supporting the infection hypothesis about lichen planus; however, electron microscopy and culture failed to reveal bacteria (Whitten, 1970). In a past study doxycycline produced modest results in treating oral lichen planus (Ronbeck *et al*., 1990). In early studies, oral metronidazole was found to be effective in patients with lichen planus who had concomitant intestinal amebiasis or giardiasis (Shelley and Shelley, 1984). It was hypothesized that in these patients the eradication of the infections was responsible for these treatments. In an another report, oral metronidazole was also found to be effective in patients with idiopathic lichen planus who had no associated protozoal infections (Buyuk and Kavala, 2000). Metronidazole has a limited spectrum of activity that encompasses various protozoans and most Gram-negative and Gram-positive anaerobic bacteria (Freeman *et al*., 1997). Moreover, it has anti-inflammatory activity and may be beneficial in treatment of rosacea and acne by inhibition of neutrophil-generated inflammatory mediators (Nishimuta and Ito, 2003; Akamatsu and Horio, 1998). Oral metronidazole suppresses granuloma formation around the parasitic eggs which suggests that it can suppress cell-mediated immunity (Grove *et al*., 1977). To the best of our knowledge, up to date, there is not a report on the comparison of these antibiotic drugs and administration them exclusively in idiopathic oral lichen planus.

Twenty patients with asymptomatic biopsy-proven OLP (11 men 9 women: Mean±SD age 45.45±15.85 years, range 15-80) how applied to the Oral Medicine Department of Mashhad University of Medical Sciences during the time period of September 2005 to May 2006 have been chosen to participate in this study. The inclusion criteria required a biopsy-proven untreated OLP of every type with no symptoms. The exclusion criteria included pregnancy, lactation, previous treatments, unilateral lichenoid reactions, presence of dysplasia in lesions, history of drinking alcohol in at least 1 month prior to the study, smoking, systemic disease, use of systemic medications and hypersensitivity to the metronidazole and doxycycline. Patients with any associated symptom of OLP (e.g., pain) or patients who treated before were excluded. The protocol was approved by the ethics committee of Mashhad University Of Medical Sciences and written informed consents were obtained from all patients. Then special forms containing demographic information, lesion types and measurements filled for every patient. Patients randomly divided into two groups and a double blind randomize control trial was performed. Each patient underwent a laboratory investigation including complete blood examination before treatment. No patient had gastrointestinal symptoms. For accurate assessment of remission, Target lesions were initially evaluated by grid measurement. Comparing to the initial size decrease to 30% was attributed to no response. Decreases 30 to 50% were attributed to partial remission and entire elimination of lesions attributed to complete remission. All clinical evaluations were performed by a member of the study team who was blinded to treatment assignment. Efficacy assessment were performed before (baseline), during treatment period (week 2) and after the treatment period (week 4). In this study 250 mg tablets of metronidazole (Tehranshimi, Tehran, Iran) and 100 mg capsules of doxycycline (Irandaru, Tehran, Iran) were utilized. The dosage for metronidazol was 1 tablet mane and 1 tablet nocte, for doxycyclin was 2 capsule daily, 1 capsule mane and 1 capsule nocte. Patients were advised to ingest each tablet/capsule with a full glass of water and not to lie down for fifteen minutes after that and were informed not to drink, eat or smoke for 1 h after. Also they were asked to confer back with the ora disease department if they had any kind of side effect. Also patients laboratory tests including Complete Blood Examination (CBE) and liver function test were performed at the end of fourth week to monitor side effects. Statistical analysis was performed by using SPSS 10.0 program (SPSS Inc, USA). Comparing of qualitative data was performed by Mann-Whitney test. Differences were considered to be significant when $p<0.05$.

All enrolled patients completed the study. The doxycycline group included 10 patients (5 female, 5 male, Mean±SD 42.60±13.83) Two patients had erosive oral lichen planus, one patient had atrophic oral lichen planus, two patients had erosive and reticular oral lichen planus, two patient had atrophic and reticular oral lichen planus and three patients had reticular oral lichen planus solely. Another group included 10 patients treated with metronidazole (5 female, 5 male, Mean±SD 48.30±17.92). One patient had erosive lichen planus, 2 patients had erosive and reticular lichen planus, 3 patients had atrophic and reticular lichen planus and 4 patients had reticular lichen planus.

Table 1: Distribution of improvement ratio in metronidazole and doxycycline groups

	Groups		
Improvement ratio	Metronidazole	Doxycycline	p
Complete remission	1(10%)	-	0.503
Partial remission	1(10%)	1(10%)	
No response	8(90%)	9(90%)	

Statistically significant difference was not seen between the two groups in respect to response to the therapy ($p>0.05$, $p = 0.503$)

At the end of the first fifteen days, in the metronidazole group one (10%) patient showed partial remission and nine (90%) patients showed no response to metronidazole therapy. Also in the doxycycline group one (10%) patient showed partial remission and nine (90%) patients showed no response. At the end of fourth week, in the metronidazole group, complete remission was obtained in one (10%) patient how had reticular form of oral lichen planus; partial remission was observed in one (10%) patient how had erosive and reticular oral lichen planus and eight (80%) patients showed no response to metranidazole therapy. In the doxycycline group at the end of fourth week one (10%) patient how had reticular form of oral lichen planus showed partial remission and nine (90%) patients showed no response. The overall response rates were not statistically different between the groups at the endpoint of therapy (Table 1). No patient at the end of the trial had burning sensation, pain or other discomfort. There were no significant changes in CBE and liver function test after four weeks of treatment in either group. Both drugs were well tolerated and no side-effects were reported from the subjects in either group.

Many studies have investigated and supported the role of immune system in pathogenesis of oral lichen planus. Cell-mediated immune dysfunction is implicated in the complex ethiopathogenesis of oral lichen planus. The immunologic process results in vascular degeneration and liquefaction of the basal cells. The large amount of cytokines released by affected keratinocytes and the associated inflammatory elements plays a key role in the selective recruitment of the T lymphocyte. T-cell dominated infiltrate in the sub epithelial region, which characterizes OLP, induced further release of chemokines and cytokines belonging to either the Th1 or Th2 groups (Thornhill, 2001).

In a previous study performed by Ronbeck *et al.* (1990), in a group of patients with desquamative gingivitis, six patients with oral lichen planus were treated with doxycycline monohydrate at 100 mg daily for 3 weeks. This derivative of tetracycline produced only modest result. One patient improved dramatically, three patients improved slightly and two patients were either unchanged or worse after the therapy. The benefits of this drug most likely are due to its anti inflammatory action and not to its anti bacterial activity.

Shelley and Shelley (1984) are the first investigators who described metronidazole as a treatment agent for lichen planus associated with urinary tract infection. They thought that efficacy of metronidazole for lichen planus was by eradication of focal infection. Later, Wahba-Yahav (1989) treated one patient with generalized lichen planus and chronic amebiasis with metronidazole). The same author later published a study representing that metronidazole treatment was effective for patients with idiopathic Lichen planus who did not have concomitant protozoal infections in their intestinal or genital tracts.In addition to formerly cited mechanism, he suggested that inhibition of cell-mediated immunity might be involve (Wahba-Yahav, 1995). Buyuk and Kavala (2000) reported that metronidazole was effective in idiopathic cutaneous and oral lichen planus with complete response rates of 78.9 and 42.8%, respectively. Ayse and Sirin (2005) reported that metronidazole was effective in idiopathic cutaneous lichen planus with complete response rate of 50% but similar to the previous study the response rate of therapy in oral lesions were lower than in the cutaneous lesions and only 25%.

In this study, both metronidazole and doxycycline are not much effective, in the metronidazole group only one (10%) patient achieved complete remission and in the doxycycline group no patient obtained complete remission. It might be because of our inclusion criteria that our patients had no symptoms and they had only oral form of disease. This observation is consistent with the reports that oral lichen planus has a higher tendency for chronicity and is more recalcitrant than cutaneous lichen planus. Present study suggest that metronidazole and doxycycline are not good therapeutic choices for oral lichen planus.

REFERENCES

Akamatsu, H. and T. Horio, 1998. The possible role of reactive oxygen species generated by neutrophils in mediating acne inflammation. Dermatology, 196 (1): 82-85.

Ayse, T.M. and Y. Sirin, 2005. A comparison of the efficacy of enoxaparandyacute; n with oral metronidazole in idiopathic lichen planus. Int. J. Dermatol., 3 (1): 12-15.

Buyuk, A.Y. and M. Kavala, 2000. Oral metronidazole treatment of lichen planus. J. Am. Acad. Dermatol., 43 (2 Pt 1): 260-262.

Dissemond, J., 2004. Oral lichen planus: An overview. J. Dermatol. Treat, 15 (3): 136-140.

Freeman, C.D., N.E. Klutman and K.C. Lamp, 1997. Metronidazole. A therapeutic review and update. Drugs, 54 (5): 679-708.

Grove, D.I., A.A. Mahmound and K.S. Warren, 1977. Suppression of cell-mediated immunity by metronidazole. Int. Arch. Allergy Applied Immunol., 54 (5): 422-427.

Middel, P., U. Lippert, K.M. Hummel, H.P. Bertsch, M. Artuc, S. Schweyer and H.J. Radzun 2000. Expression of lymphotoxin-alpha by keratinocytes: A further mediator for the lichenoid reaction. Pathobiology, 68 (6): 291-300.

Nishimuta, K. and Y. Ito, 2003. Effects of metronidazole and tinidazole ointments on models for inflammatory dermatitis in mice. Arch. Dermatol. Res., 294 (12): 544-551.

Ronbeck, B.A., P.O. Lind and P.S. Thrane, 1990. Desquamative gingivitis: Preliminary observations with tetracycline treatment. Oral Surg. Oral Med. Oral Pathol., 69 (6): 694-697.

Shelley, W.B. and E.D. Shelley, 1984. Urinary tract infection as a cause of lichen planus: Metronidazole therapy. J. Am. Acad. Dermatol., 10 (5 Pt 2): 5-7.

Thornhill, M.H., 2001. Immune mechanisms in oral lichen planus. Acta Odontol. Scand., 59 (3): 174-177.

Wahba-Yahav, A.V., 1989. Intestinal amebiasis, lichen planus and treatment with metronidazole. J. Am. Acad. Dermatol., 20 (6): 1128-1129.

Wahba-Yahav, A.V., 1995. Idiopathic lichen planus: Treatment with metronidazole. J. Am. Acad. Dermatol., 33 (2 Pt 1): 301-302.

Whitten, J.B., 1970. Intraoral lichen planus simplex: An ultrastructure study. J. Periodontol., 41 (5): 261-267.