Acta Dermatovenerol Croat 2014;22(4):250-258 ORIGINAL SCIENTIFIC ARTICLE

NAVS Naphthalan for the Treatment of Oral Mucosal Diseases – A Pilot Study

Ana Andabak Rogulj[1], Denis Brkić[2], Iva Alajbeg[3], Emir Džanić[4], Ivan Alajbeg[1,5]

[1]Department of Oral Medicine, School of Dental Medicine, University of Zagreb; [2]Altiora CRO; [3]Department of Prosthodontics, School of Dental Medicine, University of Zagreb, Zagreb; [4]Podravka R&D, Koprivnica; [5]Clinical Hospital Centre Zagreb, Department of Dental Medicine, Zagreb, Croatia

Corresponding author:
Professor Ivan Alajbeg, MD, PhD
University of Zagreb School of Dental Medicine
Department of Oral Medicine
Gundulićeva 5
10 000 Zagreb
Croatia
alajbeg@sfzg.hr

Received: March 21, 2014
Accepted: August 1, 2014

SUMMARY "Non-Aromatic Very rich in Steranes" (NAVS) naphthalan is a purified natural oil derivative, abundant in steranes (geogenic „steroids"). The purpose of this study was to evaluate the effectiveness of NAVS in the treatment of oral lichen planus (OLP) and recurrent aphthous stomatitis (RAS). We used NAVS oil in adhesive paste in 11 patients with clinically and histologically proven OLP (open label), and in 7 patients with RAS (double blind randomized; topical betamethasone in adhesive paste used as control). The severity of the OLP lesions was objectively scored. The number and diameter of RAS lesions were assessed on days 0, 3, and 5. The intensity of pain and discomfort was determined using visual analogue scale (VAS) and „Oral health impact profile" (OHIP-14) before and after therapy. OLP cumulative activity scores on days 0 and 28 were 101.5 and 48.5, respectively (t=5.99; *P*=0.0001). Using NAVS for 28 days resulted in 52.2% overall clinical improvement. Cumulative OHIP-14 scores on days 0 and 28 were 210 and 142, respectively (t=5.65; *P*=0.0002). Out of a total of 7 patients with RAS, 4 of them were treated with NAVS and 3 with topical corticosteroids. There were no statistically significant differences in improvement rate between the two groups (lesion number (day 3 *P*=0.29; day 5 *P*=0.32); lesion diameter (day 3 *P*=0.64; day 5 *P*=0.74)). NAVS successfully reduced the clinical signs and symptoms of OLP, and reduced the number, diameter, and symptoms in patients with RAS, statistically comparable with corticosteroids.

KEYWORDS: naphthalan, non-aromatic; therapy, topical; lichen planus, oral; aphthous stomatitis, recurrent; oral health impact profile; visual analogue scale

INTRODUCTION

Special types of mineral oils have been used for centuries as medicinal agents in wound healing and management of skin diseases (1). Nonaromatic naphthalan (NAVS) is a purified natural oil derivative, abundant in steranes (geogenic „steroids"), which were indicated as potential bioactive agents with healing

effects (2-8). Some studies indicated the structural similarity of geogenic steranes to bioactive natural and synthetic steroids (vitamins, steroid hormones) (8). Owing to these properties, this product has a potential role in treatment of oral mucosal diseases. Based on the literature data, NAVS was studied very extensively both *in vitro* and *in vivo* in animal models and in humans (5,7-9). Studies of genotoxicity, mutagenicity, microbiological safety, the content of heavy metals and non-metals, and irritability showed application was completely safe, regardless of the dose (4). Previous clinical studies in dermatological patients demonstrated favorable therapeutic effect, without local or systemic side effects (5,10). The origin of NAVS is an ordinary naphthalan, which has been used for decades as balneotherapy in the "Naftalan" Special Hospital for Medical Rehabilitation Ivanić Grad, without side effects and impact on biochemical or hematological parameters (5,9).

Today, topical corticosteroids are the mainstay of the management of oral immune mediated diseases. Corticosteroids commonly used in the treatment of the oral mucosal diseases are betamethasone dipropionate, clobetasol propionate, fluocinonide, and triamcinolone acetonide, the last one being often applied by intralesional injections in cases of erosive oral lichen planus (OLP) and for major aphthous ulcers (11). Carrozzo and Gandolfo (12) have listed empirical treatment modalities used for oral lichen planus, which besides those mentioned above include: a) corticosteroids (topical: betamethasone phosphate, betamethasone valerate, fluocinolone acetonide, fluticasone propionate, hydrocortisone hemisuccinate; systemic: prednisone, methylprednisolone); b) retinoids (topical: fenretinide, isotretinoin, tazarotene, tretinoin; systemic: acitretin, etretinate, isotretinoin, temarotene, tretinoin); c) immunosuppresive agents (systemic azathioprine, topical and systemic cyclosporine, pimecrolimus, and tacrolimus), d) others (amphotericin A, basiliximab, diethyldithiocarbamate, dapsone, doxycycline, enoxaparin (heparin derivative), glycyrrhizin, griseofulvin, hydroxychloroquine sulphate, interferon, levamisole, magnetism, mesalazine, phenytoin, photopheresis, psychotherapy, PUVA, reflexotherapy, surgery, and thalidomide). Additionally, mycophenolate mofetil has shown to be beneficial in very severe cases of mucocutaneous involvement recalcitrant to other forms of treatment (13). However, in OLP and recurrent aphthous stomatitis (RAS), topical corticosteroids are indicated as the first line of treatment to reduce inflammation and pain, generally without causing systemic adverse effects (14,15). The risks of short-term use of topical corticosteroids are clinically insignificant, while their long-term use is not recommended because of side effects, e.g. mucosal atrophy, secondary candidal infection, possible systemic absorption, and suppression of the adrenal glands (16). Considering these side effects of prolonged standard therapy and the frequent need for continuous treatment of chronic and recurrent oral mucosal diseases, the purpose of this study was to evaluate NAVS as an alternative treatment modality. The aim was to assess NAVS efficacy on clinical and symptomatic improvement of OLP and RAS, and to compare it with topical corticosteroids in patients with RAS.

MATERIAL AND METHODS

The study was conducted at the Department of Oral Medicine, University of Zagreb School of Dental Medicine. We included 18 patients in total, of which 11 patients with oral lichen planus (OLP) and 7 with the diagnosis of recurrent aphthous stomatitis (RAS). This study was approved by the Ethical Committee of the University of Zagreb School of Dental Medicine, and informed consent was obtained from every patient. The part of the study pertaining to patients with OLP was conducted in an open label manner. Seven patients with RAS were included in the double-blind randomized clinical trial comparing the effects of NAVS with topical steroids. Exclusion criteria were: patients younger than 18 years, hematological deficiencies, diseases of the hepatobiliary system, lichenoid reactions to amalgam and drugs, pregnancy, inflammatory bowel disease, immune dysfunction, current concomitant systemic or local anti-inflammatory therapy (corticosteroids, NSAIDs, etc.) (16-19). Routine hematological and biochemical tests were performed and data were collected through medical history. Inclusion criteria of this study were: patients with clinically and histologically proven OLP (20) and patients with RAS (according to Lehner, 2 or more episodes per year) (21). All patients involved in the study had the active phase of the disease at the start of their therapy.

NAVS formulation was prepared by mixing NAVS naphthalan oil and Stomahesive powder (ConvaTec) in volume ratio 2:1.

OLP patients were treated with topical NAVS oil in adhesive paste, three times per day for 4 weeks. The severity of the OLP lesions was objectively scored according to Pibooniyom *et al.* (22) on days 0 and 28 of the therapy. Participating clinicians were previously adjusted for inter- and intra-observer reliability for OLP clinical scoring. One clinician assessed patients on admission and the other after 28 days of treatment, in order to minimize the inherent bias of an open label study.

RAS patients were randomly divided into two groups: test and control group. The test group was treated with topical NAVS oil in adhesive paste, three times per day for 1 week, and the control group was treated with 0.05% betamethasone dipropionate ointment (Beloderm, Belupo) in adhesive paste (mixed 1:1), three times per day for 1 week. The number and diameter (in millimeters, using periodontal calibrated probe) of RAS lesions was assessed on days 0, 3, and 5 (23). In all patients, the intensity of pain and discomfort was determined using visual analogue scale (VAS) and „Oral health impact profile" (OHIP-14) before and after therapy (23,24). A photograph of the lesion was taken before and after the therapy. Randomization of RAS patients was performed by a registered nurse, and the assessing clinician was blinded to assigned treatment modality. After completion of the investigation, the randomization code in RAS cases was opened. Effects of the therapy was compared between groups (NAVS and corticosteroids) by t-test for independent samples. T-test for dependent samples was used to assess the effect of therapy in patients with OLP (before and after treatment).

RESULTS

OLP patients

The mean values of OLP activity scores on days 0 and 28 of the therapy are presented in Table 1.

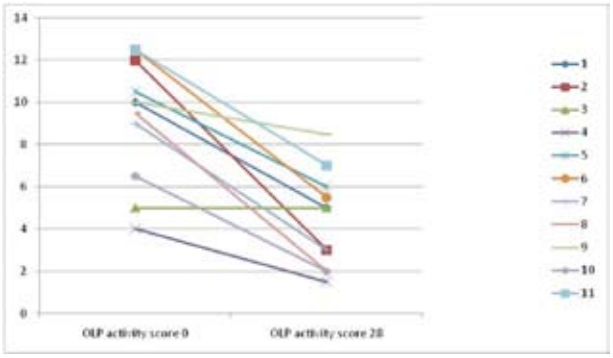

Figure 1. OLP activity scores for each patient before and at the end of treatment (on day 0 and day 28).

T-test for dependent samples showed a statistically significant reduction of hyperkeratosis, erythema, and ulceration after administration of NAVS 3 times per day for 28 days. OLP cumulative activity scores of all patients on days 0 and 28 were 101.5 and 48.5, respectively (t=5.99; *P*=0.0001). Using NAVS for 28 days resulted in 52.2% overall clinical improvement.

OLP activity scores for each patient before and at the end of treatment are presented in Figure 1.

Figures 2 and 3 show clinical improvement in 2 OLP cases after treatment with NAVS.

Oral health related quality of life assessment was determined using OHIP-14 on day 0 and 28. Cumulative OHIP-14 scores of all patients with OLP on days 0 and 28 were 210 and 142, respectively (t=5.65; *P*=0.0002). Using NAVS for 28 days resulted in 32.4% overall improvement of OHIP-14. Figure 4 presents OHIP-14 scores for each patient before and at the end of treatment.

Daily subjective symptoms were assessed using VAS. A higher value indicates a more severe painful condition. Results are shown in Table 2. Cumulative amount of VAS on days 0 and 28 were 257 and 62, respectively. This is a reduction of 75.88%.

RAS patients

Out of total 7 patients with RAS, 4 of them were allocated to treatment with NAVS and 3 to treatment with topical corticosteroids. There were no statistically significant differences in improvement rates between the two groups expressed by a percentage of the residual number of lesions in all patients (day 3 *P*=0.29; day 5 *P*=0.32) and percentage of residual lesion diameter (day 3 *P*=0.64; day 5 *P*=0.74) of all patients. The percentages of the residual number of lesions are presented in Table 3 and Figure 5.

Figure 6 shows a case of a patient with treated with NAVS, and Figure 7 a case of a patient with RAS treated with corticosteroids. There is a similar pattern of improvement in both patients after 5 days of treatment.

The percentages of residual lesion diameter are presented in Table 4 and Figure 8.

Table 1. OLP Activity score on days 0 and 28 and t-test for dependent samples (t=5,99, *P*=0,0001)

	N	Mean	Median	Minimum	Maximum	Variance	Std.Dev.	Std.Err.
OLP activity score 0	11	9.23	10.00	4.00	12.50	8.47	2.91	0.88
OLP activity score 28	11	4.41	5.00	1.50	8.50	5.19	2.28	0.69

	Mean	Std.Dv.	N	Diff.	Std.Dv.	t	df	p
OLP activity score 0	9.23	2.91						
OLP activity score 28	4.41	2.28	11	4.82	2.67	5.99	10	0.000134

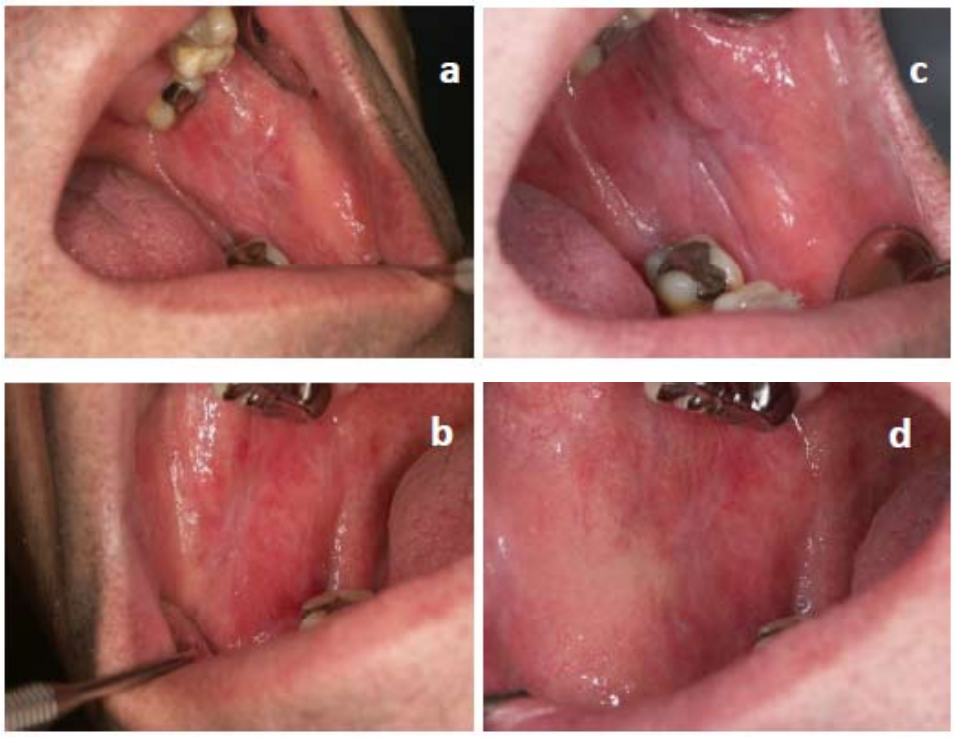

Figure 2. Patient with OLP on day 0 (a and b) and on day 28 (c and d) of NAVS treatment. Initial erythema has decreased.

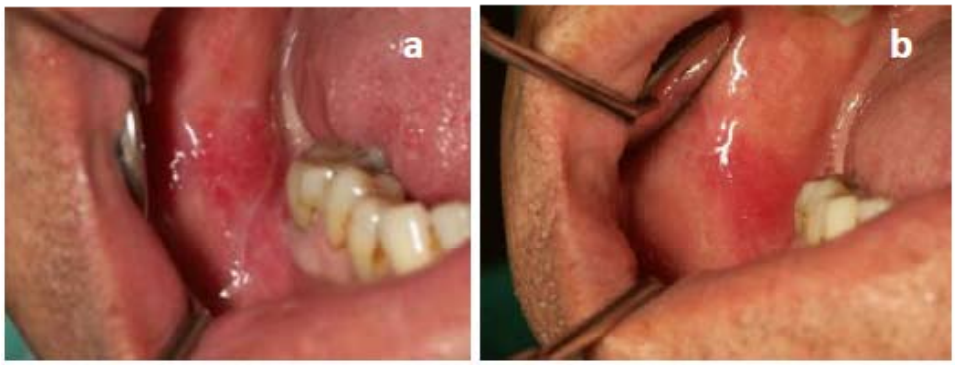

Figure 3. Patient with OLP on day 0 (a) and on day 28 (b) of NAVS treatment. Initial erythema and mucosal „atrophy" has decreased.

Subjective symptoms were assessed using VAS before and 7 days after beginning of therapy. A higher value indicates a more severe painful condition. No statistically significant differences in VAS were found between two groups (P=0.97) (Figure 9). No adverse reactions were noted.

DISCUSSION

Currently, topical steroids are the "gold standard" for treatment of many immune mediated oral diseases, including those included in this study. Because of the chronic and/or recurrent nature of those diseases, topical steroid usage often needs to be long-lasting, sometimes even lasting for years. However, topical steroid long-term usage is limited due to mucosal

Table 2. VAS on days 0 (1st week 1st day) and 28 (4th week 7th day) in patients with OLP and results of t-test for dependent samples (t=4,16, P=0.002)

	Mean	Std.Dv.	N	Diff.	Std.Dv.	t	df	p
1st week 1st day	23.36	13.84						
4th week 7th day	5.64	10.03	11	17.73	14.11	4.17	10	0.001925

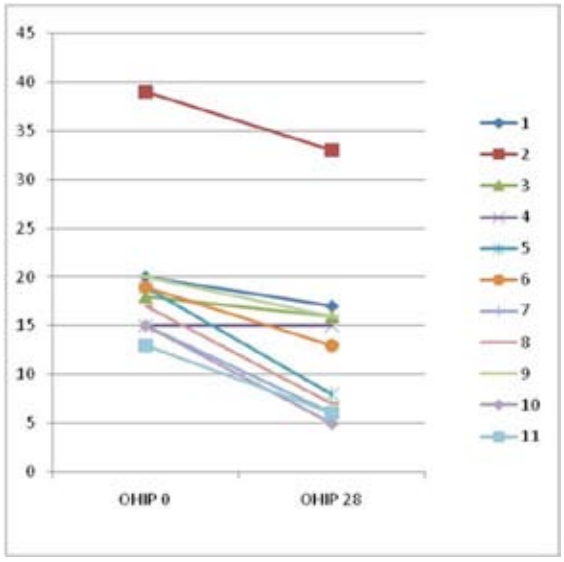

Figure 4. OHIP-14 scores for each patient with OLP before and at the end of treatment (on day 0 and day 28).

atrophy, oral candidiasis, systemic absorption, and adrenal suppression (16). Lo Muzio *et al.* reported that topical administration of 0.05% clobetasol propionate applied in different vehicles gave significant remission of the OLP and RAS lesions, but they also reported oral candidiasis occurring in 7 out of 18 patients treated with clobetasol in an adhesive denture paste (16). The persistent contact of topical steroids with oral mucosa probably causes local immunosuppression and leads to candida infection. Therefore, Carbone *et al.* proposed topical corticosteroids in association with miconazole and chlorhexidine for the long-term management of atrophic-erosive oral lichen planus, which is useful and safe prophylaxis against oropharyngeal candidiasis (25). Gonzalez-Moles *et al.* also found clobetasol 0.05% mouthwash effective for the treatment of severe oral erosive lichen planus lesions. In a 48-week period they observed 93.3% total recovery, but five patients suffered from adverse effects (hirsutism and moon face) between

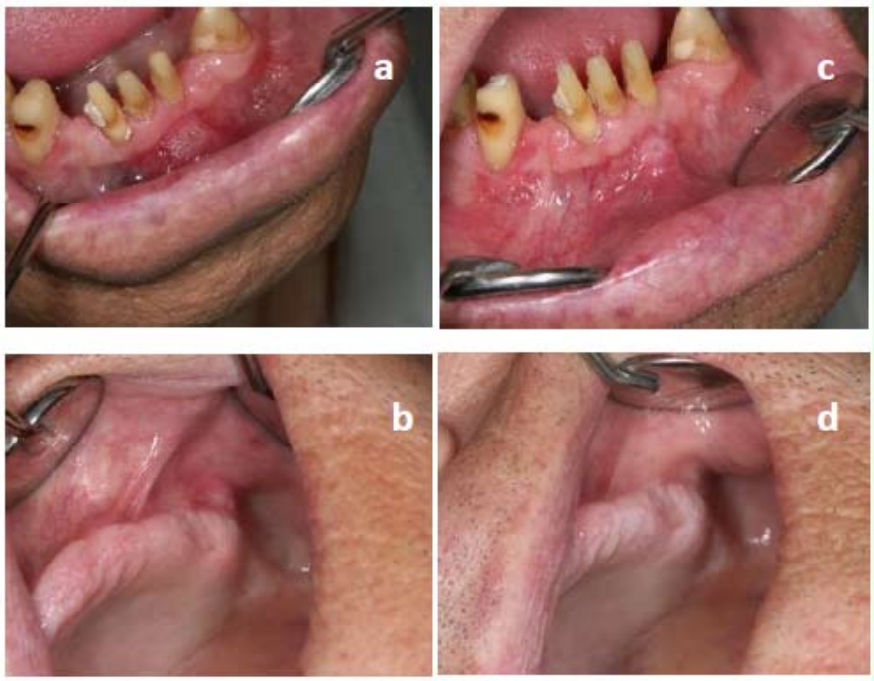

Figure 5. Patient with RAS on day 0 (a and b)and on day 5 (c and d) of NAVS treatment. Size of lesions in lower and upper vestibular areas has decreased in 5 days of treatment, similar to betamethasone treatment, as shown in Fig. 6.

Table 3. The percentage of the number of residual aphthous lesions on days 3 and 5 per group and statistical comparison between groups

% residual number	Group	Mean	Minimum	Maximum	Std.Dev.	t	p
day 3	NAVS	100.00	100.00	100.00	0.00	1.20	0.29
	cortico	88.89	66.67	100.00	19.25		
day 5	NAVS	25.00	0.00	50.00	28.87	-1.10	0.32
	cortico	44.44	33.33	50.00	9.62		

Acta Dermatovenerol Croat
2014;22(4):250-258

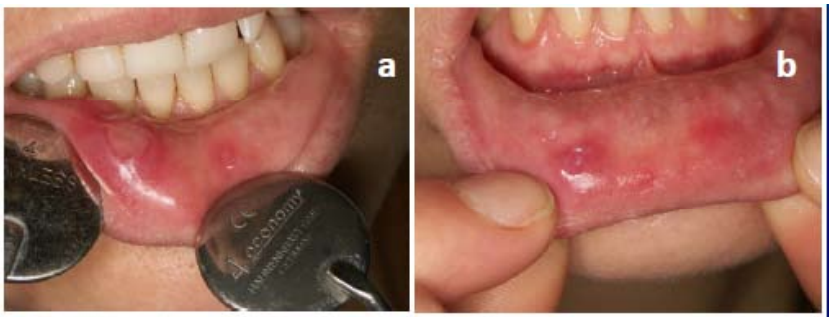

Figure 6. Patient with RAS on 0 (a) and on day 5 (b) of treatment with topical bethamethasone dipropionate. Size of lower lip lesions has decreased in 5 days of treatment, similarly to NAVS treatment as in Fig. 5.

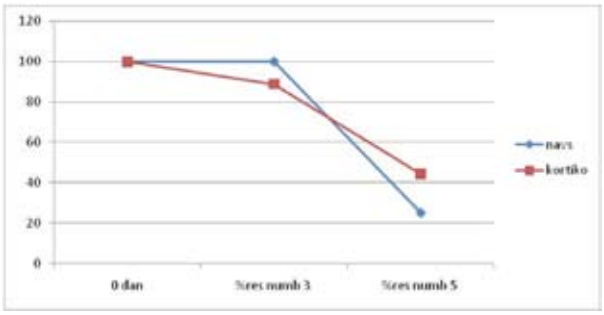

Figure 7. Reduction of the number of aphthous lesions (expressed in percentages) on days 3 and 5 (dan = day; % res numb = percentage of residual number of lesions).

week 4 and week 6 of treatment, accounting for systemic absorption (26). Other rare adverse effects were also reported, such as dry mouth, bad taste and smell, swollen mouth, and nausea (27).

In contrast, none of the aforementioned adverse reactions were observed in our patients treated with topical NAVS in adhesive paste, three times per day for 4 weeks. These results indicate safe long lasting usage of topical NAVS oil in the treatment of oral mucosal diseases, especially in chronic oral diseases such as OLP. Administration of NAVS also showed a statistically significant (P=0.0001) reduction of hyperkeratosis, erythema, and ulceration, as well as marked improvement of subjective symptoms associated with OLP. These encouraging results indicate that NAVS is a potential alternative to corticosteroids in treatment of oral mucosal diseases. Prophylactic administration of antifungal drugs is also not required. Out of a total of 7 patients with RAS (double-blind randomized clinical trial), 4 of them were treated with NAVS and 3 with topical betamethasone adhesive paste, without adverse effects. Short-term application of topical corticosteroids does not cause side effects. In cases of RAS, when recurrence frequency is not high, short time usage is indicated, and we do not foresee any occurrence of the abovementioned adverse effects. However, there are RAS cases with extremely high or constant eruption frequency, in which we need

Table 4. The percentage of residual aphthous lesion diameter on days 3 and 5 per group and statistical comparison between groups

% residual size	Group	Mean	Minimum	Maximum	Std.Dev.	t	p
day 3	NAVS	46.82	20.00	77.27	23.83	-0.50	0.64
	cortico	54.29	42.86	60.00	9.90		
day 5	NAVS	8.07	0.00	27.27	13.02	-0.35	0.74
	cortico	10.87	5.00	14.29	5.11		

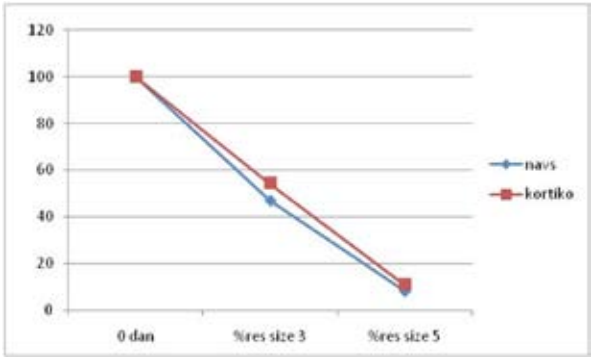

Figure 8. Reduction of the diameter of aphthous lesions (expressed in percentages) on days 3 and 5 (dan = day; %res size = percentage of residual size on days 3 and 5).

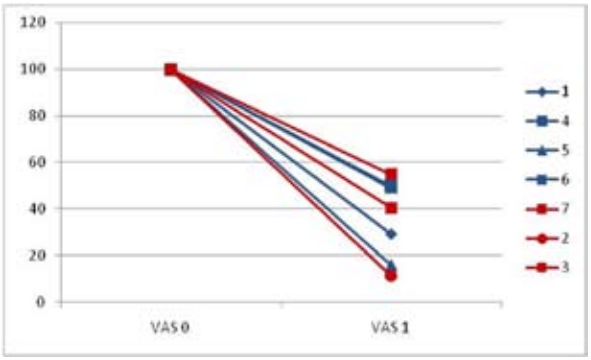

Figure 9. VAS score before the 1st application (VAS 0 = 100%) and after 7 days of treatment (VAS 1 = residual %) in patients with RAS. Blue = patients allocated to NAVS; red = patients allocated to corticosteroids.

to consider prolonged corticosteroid usage, which would eventually lead to adverse reactions. In this group of patients, a treatment modality devoid of adverse effects is required. We did not observe statistically significant differences in improvement rate between two groups according to the lesion number and lesion diameter. No statistically significant differences were found in VAS between the two groups of patients with RAS. Both clinically and symptomatically, NAVS seem comparable to topical steroid treatment of RAS. Previously published studies have tried to explain the bioactivity of naphthalan. Thaci *et al.* demonstrated its antiproliferative effect on keratinocytes and increased differentiation rate (3). Vržogić *et al.* showed its significant antiproliferative activity and ability to decrease immunocompetent cell count and reduce epidermal hyperplasia in patients with psoriasis vulgaris (28). In another study, Vržogić *et al.* demonstrated significant decrease of neovascularization rate in psoriatic lesion treated with naphthalan (29). Krnjević *et al.* also investigated the effects of naphthalan on intraepidermal proliferative activity, epidermal and dermal CD4 and CD8 lymphocyte count, intraepidermal apoptotic cell count, and antiangiogenic activity (9,10). Alajbeg *et al.* have demonstrated not only that NAVS does not cause the proliferation of the squamous cell carcinoma (SCC), but also that NAVS *in vitro* inhibits proliferation of SCC VII cells and delays tumor growth *in vivo* in the murine model, compared to controls (7). In addition, we have observed its antineoangiogenic properties in a murine oral squamous cell carcinoma model (30). Because of its inhibitory effect on intraepidermal proliferative activity, on intraepidermal and dermal inflammatory cells, as well as on neoangiogenesis, we can extrapolate those findings to our observed favorable results on OLP and RAS, as both conditions are characterized by immune cells proliferation, and OLP is additionally characterized by epithelial and endothelial proliferation (31).

There are various different naphthalan formulations available, and they are all derivative of natural oil. There are many hydrocarbon constituents, and they can not be analyzed completely. However, some important groups have been characterized (2,4-6,8,32). All naphthalan products contain steranes as a minor group of compounds, but NAVS formulation contains increased amount of steranes (thus the name "... Very rich in Steranes").

Steranes are considered to be the bioactive components in naphthalans used in the management of epithelial hyperproliferative and inflammatory diseases such as psoriasis (5). Their prospective indications may also include other immune mediated inflammatory conditions such as atopic dermatitis, rheumatoid and psoriatic arthritis (33), and now also oral lesions. Besides steranes, there are plenty of other cycloalkanes in naphthalans. Isoalkanes are present in abundance, while normal alkanes and compounds containing functional groups are present in low concentrations. Brown naphthalans contain aromatics of different structures and concentrations, making up to half of the content (32,34). As aromatics include potentially carcinogenic compounds, a common goal is to use naphthalan products containing as few aromatics as possible (34). Potentially carcinogenic polycyclic aromatics have been completely removed from NAVS (thus the name "Non-Aromatic..."), making it a safe product. To prove this, we have previously published UV/VIS spectra of NAVS, displaying the light absorption of A=0.0291 at 275 nm, which is remarkably lower than DAB 10 requirements for low-(non-) aromatic character required for medicinal paraffinic preparations (A=0.2454) (8). NAVS is a transparent, colorless, and odorless oil with a very mild pine tree fragrance, and thus applicable for oral mucosa. It is very important to bear in mind the potentially malignant nature of OLP. As an example, Australian Cancer Registry data reveal that approximately 0.2% OLP patients develop intra-oral carcinoma each year, compared with approximately 0.005% Australian adults (35). This indicates that OLP is a potentially malignant oral disorder. Thus, it is particularly important to be sure that all potentially carcinogenic polycyclic aromatics have been removed from the product that we are applying to treat OLP. Additionally, keeping in mind that NAVS has exhibited antiproliferative and antiangiogenic effects in squamous cell cancer models, one could speculate about its chemopreventive properties (7,30).

Our preliminary data were obtained using two different study designs: open label for OLP, and double blind randomized for RAS. This is the result of a process in which we primarily wanted to obtain basic preliminary data on whether NAVS affects the clinical and symptomatic course of OLP at all; hence the open label design. Encouraged by the results, we switched to a randomized controlled trial design for RAS, and were able to recruit a small group of patients. Preliminary results of this small pilot study indicate a good performance of NAVS in the treatment of OLP and RAS, statistically comparable with corticosteroid therapy for the latter. These results are encouraging, and undertaking a full scale clinical study seems worthwhile.

CONCLUSION

NAVS successfully reduced the clinical signs and symptoms of OLP; it reduced the number, lesion diameter, and symptoms in patients with RAS, statistically comparable with corticosteroids. These results indicate good performance of NAVS as a potential alternative to corticosteroids in treatment of oral mucosal diseases.

ACKNOWLEDGMENTS

This study was funded by Ministry of Science, Education and Sports of the Republic of Croatia, Grant # 065-0650445-1277 – "Nonaromatic Naphthalan – Composition Study and Bio-effects on Epithelial Tissues".

REFERENCES

1. Karaev AI, Aliev RK, Babaev AZ. Naftalanskaja neft. Moskva: Izdatel'stvo Akademiinauk SSSR;1959;5-11.
2. Alajbeg I, Krnjević-Pezić G, Alajbeg I, Smeh-Skrbin A, Vrzogić P. Comparison of the composition of some petroleum samples which may be applied for skin and mucous membrane treatment. J Pharm Biomed Anal 2000;22:75-84.
3. Thaci D, Schindewolf M, Smeh-Skrbin A, Krnjevic-Pezic G, Vrzogic P, Dobric I, *et al.* Heavy naphthen oil exhibits antipsoriatic efficacy in vivo and antiproliferative as well as differentiation-inducing effects on keratinocytes in vitro. Arch Dermatol 2000;136:678-9.
4. Alajbeg I, Dinter G, Alajbeg A, Telen S, Proštenik M. Study of Croatian non-aromatic naphthalane constituents with skeletons analogous to bioactive compounds. J Chromatogr A 2001;918:127-34.
5. Alajbeg I, Krnjević-Pezić G, Smeh-Skrbin A, Vržogić P, Vučićević-Boras V, Dobrić I, *et al.* Non-aromatic naphthalane preparation; preliminary clinical study in the treatment of psoriasis vulgaris. J Pharm Biomed Anal 2001;26:801-9.
6. Alajbeg A, Donelli D, Alajbeg I, Telen S, Šegudović N, *et al.* Characterisation of Azerbaijani and Croatian brown naphthalane. J Sep Sci 2005;28:1512-9.
7. Alajbeg I, Ivanković S, Alajbeg ŽI, Jurin M. Antiproliferative effect of non-aromatic oil fractions on squamous cell carcinoma VII: in vitro and preliminary in vivo results. Period Biol 2002;104:89-94.
8. Alajbeg I, Ivanković S, Jurin M, Alajbeg ZI, Rošin-Grget K, Cekić-Arambašin A. Non-aromatic naphtalane as a potential healing medium. Period Biol 2002;104:81-7.
9. Krnjević-Pezić G, Vržogić P, Ostrogović Ž, Smeh-Skrbin A, Dobrić I. Some hematological and biochemical parametrers in psoriatic patients treated with naphthalan. Acta Dermatovenerol Croat 1997;5:49-53.
10. Smeh-Skrbin A, Dobrić I, Krnjević-Pezić G, Vržogić P. Naphthalene in the treatment of patients with atopic dermatitis. Acta Dermatovenerol Croat 2007;15:15-9.
11. González-Moles MA. The use of topical corticoids in oral pathology. Med Oral Patol Oral Cir Bucal 2010;15:e827–31.
12. Carrozzo M, Gandolfo S. The management of oral lichen planus. Oral Dis. 1999;5:196-205.
13. Wee JS, Shirlaw PJ, Challacombe SJ, Setterfield JF. Efficacy of mycophenolate mofetil in severe mucocutaneous lichen planus: a retrospective review of 10 patients. Br J Dermatol 2012;167:36-43.
14. Miles DA, Bricker SL, Razmus TF, Potter RH. Triamcinolone acetonide versus chlorhexidine for the treatment of recurrent stomatitis. Oral Surg Oral Med Oral Pathol 1993;75:397-402.
15. Voute AB, Schulten EA, Langendijk PN, Kostense PJ, Van Der Wall I. Flucinonide in an adhesive base for treatment of oral lichen planus. Oral Surg Oral Med Oral Pathol 1993;75:181-5.
16. Lo Muzio L, della Valle A, Mignona MD, Pannone G, Bucci P, Bucci E, *et al.* The treatment of oral aphthous ulceration or erosive lichen planus with topical clobetasol propionate in three preparations: a clinical and pilot study on 54 patients. J Oral Pathol Med 2001;30:611-7.
17. Rodriguez M, Rubio JA, Sanchez R. Effectiveness of two oral pastes for the treatment of recurrent

aphthous stomatitis. Oral Dis 2007;13:490-4.

18. Nolan A, Baillie C, Badminton J, Rudralingham M, Seymour RA. The efficacy of topical hyaluronic acid in the management of recurrent aphthous ulceration. J Oral Pathol Med 2006;35:461-5.
19. Zakrzewska JM, Chan ES-Y, Thornhill MH. A systematic review of placebo-controlled randomized clinical trials of treatments used in oral lichen planus. Br J Dermatol 2005;153:336-41.
20. WHO Collaborating Centre for Oral Precancerous Lesions. Definition of leukoplakia and related lesions: an aid to studies on oral precancer. Oral Surg Oral Med Oral Pathol 1978; 46: 518-39.
21. Lehner T. Autoimmunity in oral disease with special reference to recurrent oral ulcerations. Proc R Soc Med 1968;61:515-24.
22. Piboonniyom SO, Treister N, Pitiphat W, Woo SB. Scoring system for monitoring oral lichenoid lesions: A preliminary study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99:696-703.
23. Khandwala A, Van Inwegen RG, Alfano MC. 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: I. Clinical demonstration of acceleration of healing and resolution of pain. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997; 83: 222-30.
24. Petričević N, Čelebić A, Papić M, Rener-Sitar K. The Croatian version of the Oral Health Impact Profile Questionnaire. Coll Antropol 2009; 33: 841-7.
25. Carbone M, Conrotto D, Carrozzo M, Broccoletti R, Gandolfo S, Scully C. Topical corticosteroids in association with miconazole and chlorhexidine in the long-term management of atrophic-erosive oral lichen planus: a placebo-controlled and comparative study between clobetasol and fluocinonide. Oral Dis 1999;5:44-9.
26. Gonzalez-Moles MA, Morales P, Rodriguez-Archilla A, Isabel IR, Gonzalez-Moles S. Treatment of severe chronic oral erosive lesions with clobetasol propionate in aqueous solution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;93:264-70.
27. Hegarty AM, Hodgson TA, Lewsey JD, Porter SR. Fluticasone propionate spray and betamethasone sodium phosphate mouthrinse: a randomized crossover study for the treatment of symptomatic oral lichen planus. J Am Acad Dermatol 2002; 47: 271–9.
28. Vržogić P, Jakić-Razumović J, Pasić A. Effect of naphthalan on epidermal proliferation activity and CD3, CD4, and CD8 lymphocyte count. Acta Dermatovenerol Croat 2003;11:65-9.
29. Vržogić P, Jakić-Razumović J, Lipozencić J. Naphthalanotherapy reduces angiogenetic factor in psoriatic lesion. Acta Dermatovenerol Croat 2004;12:7-11.
30. Alajbeg I, Ivanković S, Jurin M, Pirkić A, Alajbeg ZI, Cekić-Arambašin, *et al*. Antitumor activity of non-aromatic naphthalane: angiogenesis inhibition in murine oral squamous cell carcinoma. Abstracts of 7th biennal congress of European Association of Oral Medicine / Reichart, Peter (Ed.). Berlin: Quintessenz Verlags-GmbH, 2004. p. 38.
31. Scully C, Beyli M, Ferreiro MC, Ficarra G, Gill Y, Griffiths M, *et al*. Update on oral lichen planus: etiopathogenesis and management. Crit Rev Oral Biol Med 1998;9:86-122.
32. Vržogić P, Ostrogović Z, Alajbeg A. Naphthalan - a natural medicinal product. Acta Dermatovenerol Croat 2003;11:178-84.
33. Krnjević-Pezić G, Alajbeg I, Maričić G, Pašić A, Čurković B, Čeović R, *et al*. Naphthalan oil in the treatment of psoriasis and psoriatic arthritis. psoriasis forum 2012;17:23-8.
34. Alajbeg I, Brkić D, Ahel M, Telen S, Džanić E, Fingler S, *et al*. Chemical composition and physical properties of "pale yellow" naphtalan. Croat Chem Acta 2011;84:521-30.
35. Sugerman PB, Savage NW. Oral lichen planus: causes, diagnosis and management. Aust Dent J 2002;47:290-7.