Pilot study comparing triamcinolone acetonide dental paste and oraflogo gel on oral ulcerative lesions

Summary

The etiology of oral ulcerative lesions is unclear, which means there are various approaches to treatment. Some treatments are systemic, others are local. The treatment of choice for local application is triamcinolone acetonide dental paste in orabase (synthetic corticosteroid). Given the undesirable side effects arising from this therapy, researchers are trying to find an effective natural treatment. The aim of this study is to determine the local effectiveness of natural active ingredients within a base of hyaluronic acid with added natural plant extracts (under the protected name "Oraflogo gel") and to compare it with the effectiveness of the proven treatment triamcinolone acetonide in treating minor ulcers.

The study involved 22 patients with oral ulcers, half of whom were randomly selected to use triamcinolone acetonide to treat the problem, while the other half applied Oraflogo gel. The research monitored two parameters: pain reduction and ulcer size. Both treatments were applied locally in the same way. A comparison of the reduction in pain and ulcer size revealed that the effectiveness of treating minor ulcers with medically tested triamcinolone acetonide on the one hand, and hyaluronic acid with plant extracts on the other, is statistically significantly comparable both in terms of reducing the size of the ulcer itself as well as the associated pain.

Key words: minor ulcerative lesions, triamcinolone acetonide, hyaluronic acid

Recurrent aphthous stomatitis is the most common form of ulceration on the nonkeratinized mucosal surfaces of the mouth (Gallo, Mimura, Sugaya, 2009). The term comes from the Greek word "aphta" which means mouth ulcer (Wikipidea). Ulcers are usually round or oval in shape with rounded edges. The inside of the sore is deeper than the sides, is a grey or yellow colour and is surrounded by an erythematous halo. Most commonly they occur as a painful formation in the oral mucosa which affect the functioning of the stomatognathic system, such as eating, speaking, facial expressions, kissing etc (Preeti et al., 2011). The onset of the lesions usually occurs in childhood or adolescence, but it can be later in certain individuals. The size and intensity of the lesions decreases with age. There has been no evidence of differences in occurrence between the sexes (Fani et al., 2012).

After Stanley (1972), ulcerative changes are classified under three primary groups: 1. smaller (minor) 2. larger (major) and 3. herpetiform ulcers (Fani et al., 2012). The group of small ulcers encompasses ulcers with a diameter of 8 to 10 millimetres and is the most widespread, representing an estimated 80% of all occurring ulcers. They usually appear on the nonkeratinized mucosal surfaces of the mouth (labial mucosa and floor of the mouth). The ulcers usually take 10 to 14 days to heal with no scarring (Preeti et al., 2011).

The group of larger ulcers (major), includes ulcers larger than 1 cm in length and represent 10 to 15% of cases of patients with ulcers. They most frequently occur on the mucous membrane of the oral cavity, oesophagus and the soft palate. It takes over 6 weeks for this type of ulcer to heal and scars remain (Fani et al., 2012; Preet et al., 2011).

Herpetiform ulceration comprises a group of smaller ulcers (2-3mm in diameter), which join together and form larger irregular ulcers. They take 10-14 days to heal, are not preceded by vesicles and not caused by a virus. This type of ulcer most commonly occurs in older women (Preeti et al., 2011, Fani et al., 2012 and Deshmukh and Bagewadi, 2014).

Even today, it remains unclear exactly what causes oral ulcerative lesions. Predisposing factors which influence the occurrence and development of ulcers are genetic predisposition, psychological stress, immune system disorders, trauma to the oral mucosa, smoking, certain medications, vitamin deficiency (B12, folic acid), iron deficiency, gluten intake in patients with gluten-sensitive enteropathy: inflammatory bowel disease (Shakeri et al., 2009), ulcerative colitis and Crohn's disease (Jurge et al., 2006). Jurge et al. (2006) discovered that frequently occurring ulcers are linked to the use of the common surfactant and detergent (sodium lauryl sulfate) in toothpaste. They therefore recommend that people prone to ulcers avoid using products containing this chemical in the oral cavity.

The pathogenesis of ulcers involves a lot of diverse microorganisms and research published on this topic is contradictory. The hypothesis that the microorganism oral streptococcus could be directly involved in the pathogenesis of oral ulcers has been partially confirmed. The pathogenesis of oral mucosal ulceration includes these microorganisms either directly or as an antigenic stimulus that induce the production of antibodies, which then cross-react with the oral mucosa. The suspected pathogen was the L- form of alpha-haemolytic streptococcus (Streptococcus sanguis). However, Hoover and colleagues (1986) revealed a low level of cross-reaction and therefore classified it as a nonspecific cause.

Gram-negative Helicobacter pylori, which causes gastritis and chronically infected ulceration of the duodenum, was suspected to cause ulcerative lesions, as a high concentration of it was found in the supragingival dental plaque (Lemiola-Virtanen et al., 1995). Later, Porter and colleagues (1997) discovered that there are no major differences in the level of immunoglobulin IgG against Helicobacter pylori between patients with ulcers, those with other types of lesions on the oral mucosa, and healthy people (Porter et al., 1997).

In the etiopathogenesis of recurrent oral ulcers, the researchers also included various viruses, given that the characteristics of ulcerative lesions are indicative of infectious etiology, such as recurring ulceration, lymphocytic infiltration, increased vascular permeability and the presence of auto-antibodies. Antibodies characteristic of viral infections in animals were found in the infiltrate (Hooks, 1978). Biopsies of the oral mucosal ulcers revealed the presence of human cytomegalovirus DNA (HCMV), but they were unable to rule out the possibility of the super-infection of cytomegalovirus, present in the saliva (Lemiola-Virtanen et al., 1995). Proof of the presence of the Eppstein-Barr virus in the genome of the polymerase chain reaction in pre-ulcerative oral aphthous tissues, supports the hypothesis that this virus is responsible for causing ulcerative lesions (Sun et al., 1998).

TNF-α (tumor necrosis factor) has also been proven to play a role in the occurence of ulcerations on the oral mucosa. It is one of the most important cytokines, which play a part in the appearance of new ulcers. The proof is in the efficacy of the regulatory immune system response. The drug thalidomide reduces TNF-α activity by decomposing its mRNA (Jacobson et al., 1997), whilst the active substance pentoxifylline prevents TNF-α synthesis (Zabel et al., 1993).

Ulcerative oral lesions have functional consequences such as the obstruction of speech, eating, swallowing and a low sense of well-being, which can affect our ability to work effectively. Consequently, the occurence of ulcers can drastically reduce quality of life. Certain individuals suffer from chronic recurrent ulcers.

Unclear etiology leads to various different types of treatment for ulcerative lesions.
Treatment for small ulcerative lesions can be divided into various points of application or a combination of the following: improved oral hygiene, protective deposits, antiseptics, antibiotics, hormones, local anaesthetic and steroid therapy. Topical treatment reduces pain and speeds up the healing process. Given that systemic treatment has side effects, localised therapy is the treatment of choice for smaller ulcers (Meng et al., 2009).

The preferred medication for topical application is the dental paste triamcinolone acetonide in orabase. It is a synthetic corticosteroid which is eight times stronger than prednisone. It comes in a paste form and has proved to have satisfactory results; however, it is suspected to cause side effects (Fani et al., 2012; Miles et al., 1993; Deshmukh and Bagewadi, 2014). Triamcinolone acetonide is a fluoride synthetic corticosteroid. It is used as a paste or concentrated gel (0,1%) for topical application to the ulcerated area.

The level of systemic drug absorption from the area of topical application varies from 1% on the surface of the arm and knee, to 36% on the face, eyelids and genitals. The systemic absorption rate also increases if the skin or mucosa is damaged, inflamed or irritated (Khandwala et al.,1997). The metabolisation of the topically applied local corticosteroid occurs in the skin or mucosa. Smaller amounts, when systemically absorbed, are metabolised in the liver. The side effects of topical corticosteroid include burning, itching, irritation at the point of application, dry skin/mucosa, inflammation of the hair follicles on the skin, excessive hairiness, hyperpigmentation, dermatitis around the oral cavity or on the skin in general, contact allergies, secondary infections and mucosal or skin atrophy (Khandwala et al.,1997).

In order to avoid the side effects of corticosteroid, researchers are still looking for an alternative substance which can be applied locally to ease pain and rapidly heal the mucosa. Tried and tested substances include chlorhexidine digluconate (Miles et al., 1993), turmeric (Deshmukh and Bagewadi, 2014), phenytoin (Fani et al., 2012), Ageratina pichinchensis plant extract (Romero -Cerecero et al., 2015), sucralfate (Rattan et al., 1994), thalidomide (Jacobson et al., 1997) and the hyaluronic acid preparation Oraflogo gel (Kuliš et al., 2014). Hyaluronic acid is a biomaterial and the most well recognised carbohydrate component of the extracellular matrix. It contains polycarbophil- a protein which adheres to the moist mucous membrane (Koray et al., 2016).

The aim of this pilot study was to determine the local effectiveness of natural active ingredients in a base of hyaluronic acid and natural plant extracts ("Oraflogo gel"), in comparison to the tried and tested medication triamcinolone acetoni-

de (0,1%) in orabase, for treating ulcerative lesions.

Our study proposed two hypotheses which were confirmed:
First hypothesis: hyaluronic acid (Oraflogo gel) is just as effective at reducing the size of ulcerative lesions in the oral mucosa as corticosteroid (triamcinolone in orabase).
Second hypothesis: hyaluronic acid (Oraflogo gel) is equally as effective in reducing the pain associated with ulcerative lesions on the nonkeratinized oral mucosa as corticosteroid (triamcinolone in orabase).

Materials and methods

The pilot study involved 22 patients, each of whom had from at least two fixed dental protheses to those who had complete coverage with two dental bridges. No one had removable prostheses. The fact that all patients included in the study had the same type of dental protheses prevented different manifestations of the pathology. All patients had already suffered from ulcerative lesions in the past and we asked them to come into the clinic as soon as the ulcerative lesions appeared in the oral mucosa (no later than 48 hours after their appearance). There were 12 females and 10 males in the group, all of whom had minor to medium-size ulcers (Preeti et al., 2012; Fani et al., 2012). Males and females were divided into two equally sized groups through a draw. An almost equal division of women and men per group prevented the results being skewed by gender. The age of the patients ranged from seventeen to fifty-eight years old. The average age in the first group was 35,67±9,85 years old; in the second group it was 38,89±8,4. The patients had minor to medium-size ulcers, with a diameter of no more than 1cm, located on the nonkeratinized oral mucosa, either in the buccal mucosa, the oral vestibule or the sublingual area. Each patient had from one to six ulcers.

Patients were informed in advance that they would be part of a research group and would be treated either with the standard treatment used in most cases up until now, or with a newly tested product. None of the participants were suffering from any systemic or acute illnesses. Three had increased blood pressure which had been successfully treated. Two had been successfully treated for raised cholesterol levels in the blood. None of the others were taking any medication, using medical devices or dietary supplements. All participants complained of reduced oral function, pain when eating or speaking and hypersalivation. For all patients, the lesions were sensitive when touched, permeable and differed in temperature. All were keen to get rid of the pain as soon as possible and regain normal oral function. Participants were informed in detail beforehand about how the research and treatment was going to take place, and they then filled out a WDF questionnaire and permission form. The research was presented to and approved by the ethics commission.

After receiving patient consent, both types of topical treatment to be tested were used in the same way. The selection regarding the type of treatment was determined by a draw. Female and males were divided to ensure even representation of the sexes in each group.

The first group of eleven patients were treated with the topical dental paste triamcinolone acetonide in orabase (0,1%) (Ljubljana pharmacy d.o.o). The group was comprised of five men and six women. After thoroughly rinsing the mouth with lukewarm water and getting rid of any excess fluid, patients applied the paste directly onto the ulcerative lesion three times a day with a clean cotton wool bud. They were not allowed to eat or drink anything for half an hour after applying the treatment. The other group of eleven patients were treated with the topically applied gel comprised of hyaluronic acid and natural herbal extracts (“Oraflogo gel”, Panakea d.o.o). This group also included five men and six women. The gel was applied as detailed above for the first group. The instructions provided were also exactly the same. For the duration of the study we monitored and measured changes in pain intensity and size of the ulcerative lesion.

Participants recorded pain intensity on a daily basis using the “VAS” scale. They also estimated the reduction in the size of the ulcerative lesion in percentage terms, on the first, third and seventh day after commencing treatment. Patients measured the size of the ulcer with a metal ruler which they sterilised with 70% ethanol each time before using it. Patients with several ulcers measured the largest one with the longest diameter. The results were statistically analysed using the SPSS software package (version 14.0, Chicago, IL, USA). We used the Wilcoxon-Mann-Whitney test with normal approximation.

Results

This was a comparative study between two independent groups of patients. Each group was comprised of 11 participants. Patients in the first group were treated with the topical Oraflogo gel, those in the other group were treated in the same way but with the synthetic corticosteroid triamcinolone acetonide in orabase. During treatment we monitored the reduction in size of the ulcerative lesions and reduction in pain.

The research variables were:
1. Percentage reduction in size of ulcer: measured three times per patient- on the first, third and seventh day after starting treatment. The values were rounded off to the nearest ten, so there were 11 possible values.
2. Pain: measured five times per patient- on the first to the second day, the third and fourth day, the fifth to the sixth day, and the seventh day. Values were noted according to the VAS scale, rounded up to the nearest whole number, so there were 11 possible values.

To begin with we discovered that alongside the research variables there were also continuous random variables but rounding up the values had the effect of categorisation so we had to treat the variables as categorical. In order to compare the values of whichever variable between the two groups we therefore had to use the Wilcoxon-Mann-Whitney test with normal approximation in a form which allows for tied values (Lehmann 1975, p. 21). The number of patients in each group meets the usually applied recommendations for using normal approximation. For paired value comparisons of variables within each group we used the sign test in a form which allows for equal values (Lehmann 1975, p. 164 and recommendations of Heller et al., 2016). We also carried out several equivalence tests using Mann-Whitney statistics (Wellek, 1996 and Wellek and Hampel, 1999).

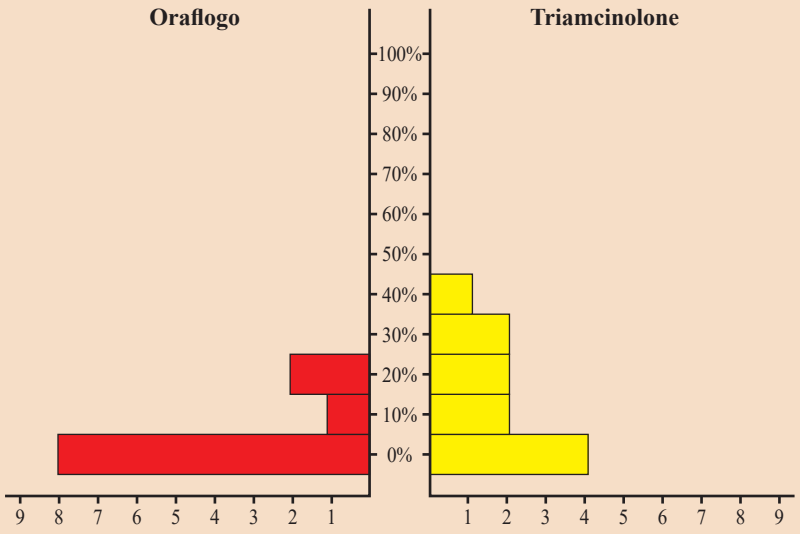
The primary random variables were:
- X_0: percentage reduction in ulcer size in the Oraflogo group at the end of the research period (the seventh day),
- X_T: percentage reduction in ulcer size in the triamcinolone group at the end of the research period (the seventh day),
- Y_0: the first minus the final value of pain level in the Oraflogo group,
- Y_T. the first minus the final value of pain level in the triamcinolone group.

The primary assumptions were:
1. The values of variable X_0 are stochastically greater or equal in value to that of variable X_T.
2. The values of variable Y_0 are stochastically greater or equal in value to that of variable Y_T.

1 Reduction in ulcer size

1.1 Frequency distribution
1.1.1 Frequency distribution in the reduction of ulcer size at the start of treatment (first day).

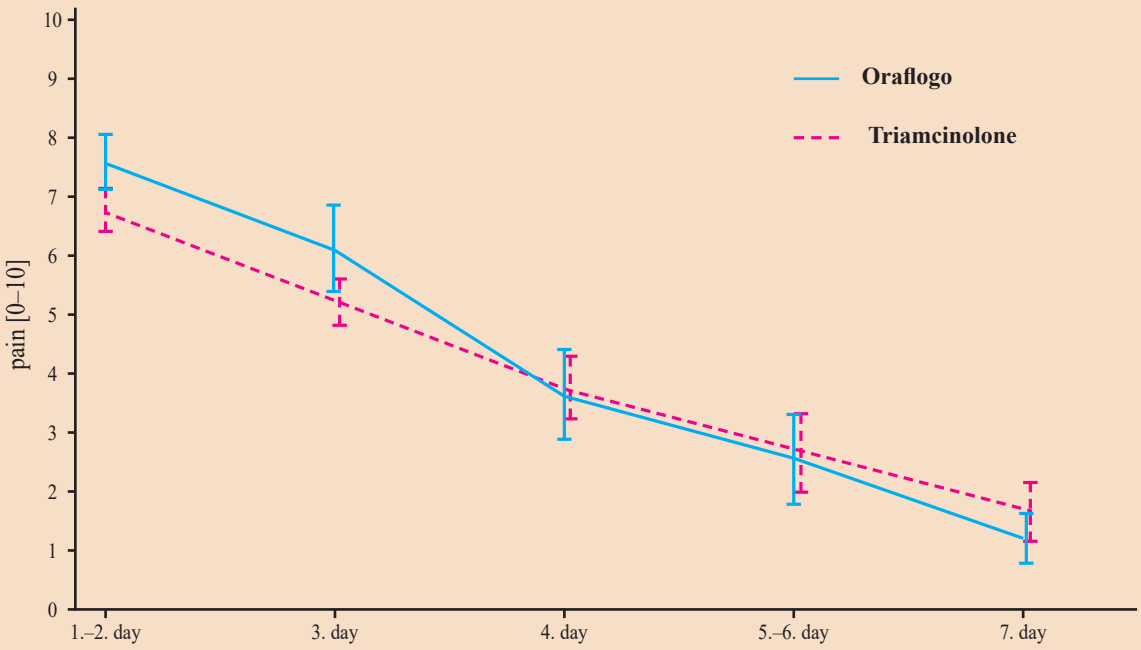
GRAF 1:
REDUCTION IN ULCER SIZE AT START OF TREATMENT



Frequency of distribution in reducing ulcer size at the start of treatment (first day). The vertical axis shows percentage reduction in ulcer size, the horizontal axis shows the number of patients.

(The horizontal axis shows the number of patients; the vertical axis shows the effectiveness in reducing the size of the ulcerative lesion).

GRAF 3:
COMPARISON OF REDUCTION IN ULCER SIZE DURING TREATMENT



Graphical representation of the percentage reduction in ulcer size, showing standard errors, during treatment with two substances (triamcinolone and Oraflogo) on the first, third and seventh day after the start of treatment.

Some of the patients reported that triamcinolone acetonide was more effective because there was a greater reduction in ulcer size on the first day of treatment with corticosteroid dental paste than with Oraflogo gel. Many of the patients using Oraflogo gel didn't report any reduction ulcer size on the first day, whereas patients being treated with triamcinolone experienced up to a 40% reduction in size. The largest reduction in ulcer size for those using Oraflogo gel was 20%, but amongst a smaller number of patients.

1.1.2 Frequency distribution in the reduction of ulcer size at the end of treatment (seventh day.

(The horizontal axis shows the number of patients; the vertical axis shows the effectiveness in reducing the size of the ulcerative lesion).

The graph shows that a larger number of patients in the Oraflogo group reported a greater reduction in ulcer size. None of the patients in the group using triamcinolone reported complete healing after seven days of treatment, whereas some in the group using Oraflogo gel did. We can therefore conclude that after seven days of treatment, Oraflogo gel is more effective.

1.2 Average values

1.3 The tables show the average values with standard error for the average in reducing ulcer size (%) during treatment: (Table 1).

TABLE 1:
REDUCTION IN ULCER SIZE DURING TREATMENT

	1. day	3. day	7. day
Oraflogo	5±2.5	28±6.4	79±4.8
Triamcinolon	15±4.3	43±4.3	62±4.4

Reduction in ulcer size (%) during treatment with the two different substances at the measured intervals (1st, 3rd and 7th day) with standard error deviation.

The results in the table show that triamcinolone was more effective in reducing ulcer size at the start, i.e. up to the third day of treatment. After that (on the seventh day) there is a turn around and Oraflogo is more effective.

(Data is cited in terms of average ± average standard error)

Average reduction in ulcer size (expressed as a percentage) during treatment as noted on the 1st, 3rd and 7th day (0% refers to the size of the ulcer at the start, 100% reduction means disappearance of the ulcer, i.e. complete healing) (Table 1, Graph 3).

The graph shows that triamcinolone was more effective at reducing ulcer size at the start of treatment, whilst Oraflogo gel was more effective in the later stages of treatment.

1.4 Statistical tests

Statistical proof of the results shown graphically above between participants treated with triamcinolone and Oraflogo to reduce ulcer size.

The sign test showed that changes between those using Oraflogo and those using triamcinolone were statistically significant ($p \leq 0{,}01$). A comparison between both groups showed that the starting values (on the first day) in the Oraflogo group were less statistically significant than the values of those in the triamcinolone group (one-sided Wilcoxon- Mann- Whitney test, $p=0{,}033$). A comparison on the third day also revealed that the in-between values in the Oraflogo group were statistically less significant than the values in the triamcinolone group (one-sided Wilcoxon- Mann- Whitney test, $p=0{,}036$). The first couple of primary variables consisted of a reduction in ulcer size in the Oraflogo group and reduction in ulcer size in the triamcinolone group at the end of the research (on the seventh day). The one-sided Wilcoxon -Mann- Whitney test revealed that the values of the Oraflogo group were statistically more significant than the values of the triamcinolone group ($p=0{,}020$).

Our hypotheses were therefore also proven to be statistically correct.

2 Pain

2.1 Frequency distribution

2.1.1 Frequency distribution of pain at start of therapy (1-2 day)

(The vertical axis shows the pain measurement (VAS); the horizontal axis shows the number of patients).
table

During the first stages of treatment some of the patients using Oraflogo gel still reported the highest level of pain intensity as measured on the VAS scale, whilst none of those being treated with triamcinolone reported such high pain intensity. The lowest level of pain as measured on the VAS scale was the same in both groups, but more patients in the triamcinolone group reported these lower pain levels. We can therefore estimate that those treated with triamcinolone experienced a greater reduction in pain at the start of treatment.

2.1.2 Frequency distribution of pain at end of treatment (7th day)

(The vertical axis shows the pain scale (VAS); the horizontal axis shows the number of patients).

At the end of the seventh day, the group treated with triamcinolone and the group treated with Oraflogo were comparable. Some patients in both groups noted the same level of pain, the highest of which was 4 on the VAS scale; the lowest level demonstrated complete disappearance of pain in both groups. A greater number of patients in the group treated with triamcinolone reported the highest level of pain, whereas the lowest level of pain i.e. no pain at all was reported by a greater number of patients treated with Oraflogo. We can therefore conclude that after seven days of treatment, Oraflogo gel was more effective than triamcinolone.

2.2 Average values

TABLE 2: REDUCTION IN ULCER PAIN DURING TREATMENT

Average level of pain during treatment

(Data are cited in terms of average ± average standard error)

The table shows comparable values in reducing pain during treatment, with both triamcinolone and Oraflogo

GRAPH 6: REDUCTION IN ULCER PAIN DURING TREATMENT

Graphical representation of pain reduction at the following times: (1-2 day, 3rd day, 4th day, 5-6 day and 7th day) for both substances on average with standard error deviations during the period of research.

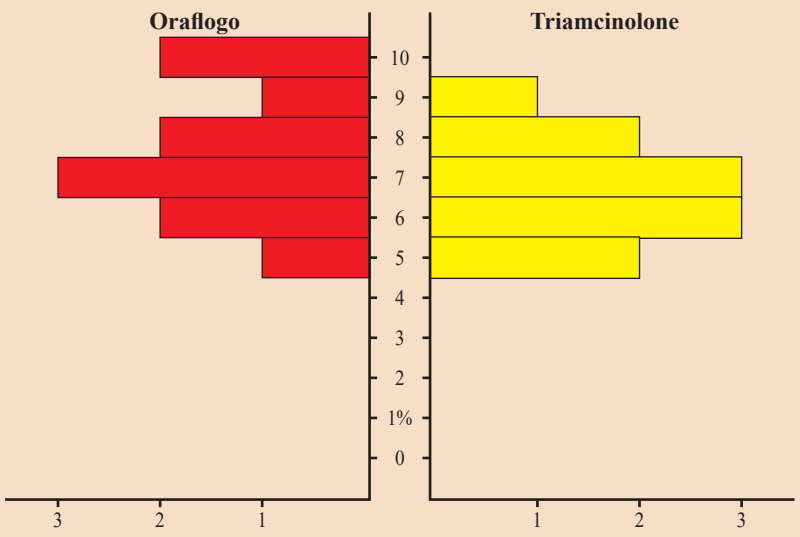
The graph reveals an almost parallel drop in pain intensity during treatment. It could be said that triamcinolone is more effective at reducing pain at the start of treatment, but Oraflogo gel is more effective after seven days of treatment, yet we were unable to prove this statistically.

2.3 Statistical tests

Comparisons between the groups during individual visits (Wilcoxon-Mann- Whitney tests) didn't reveal statistically significant differences. Equivalence tests (Wellek and Hempel) were also unable to statistically confirm equivalence during individual visits. On the basis of the tests carried out, the level of pain in both groups was comparable, but it was not possible to statistically prove the differences.

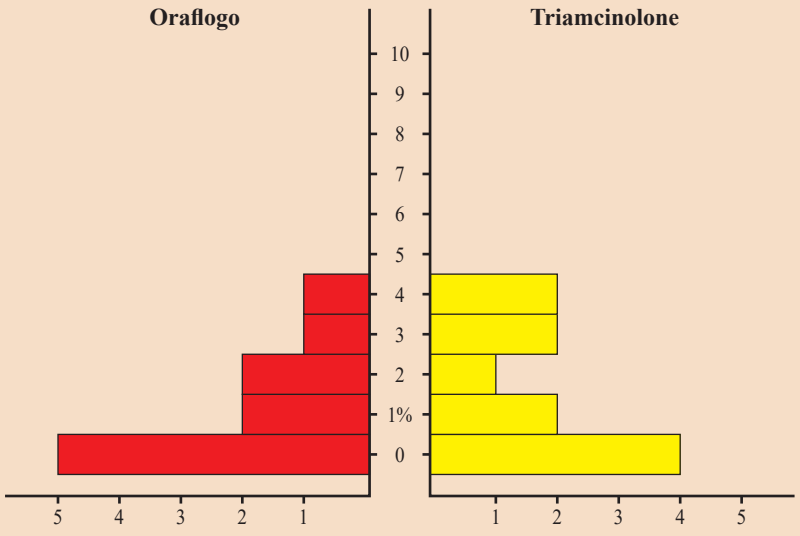
One of the primary variables was also the difference between “the starting minus the end value” in the

GRAF 4:
CLASSIFICATION OF PATIENTS INTO GROUPS BASED ON PAIN INTENSITY AT THE START OF TREATMENT



Frequency distribution of pain at start of therapy (1-2 day). The vertical axis shows the pain measurement scale (VAS); the horizontal axis shows the number of patients.

GRAF 5:
CLASSIFICATION OF PATIENTS INTO GROUPS BASED ON PAIN INTENSITY AFTER THE SEVENTH DAY OF TREATMENT



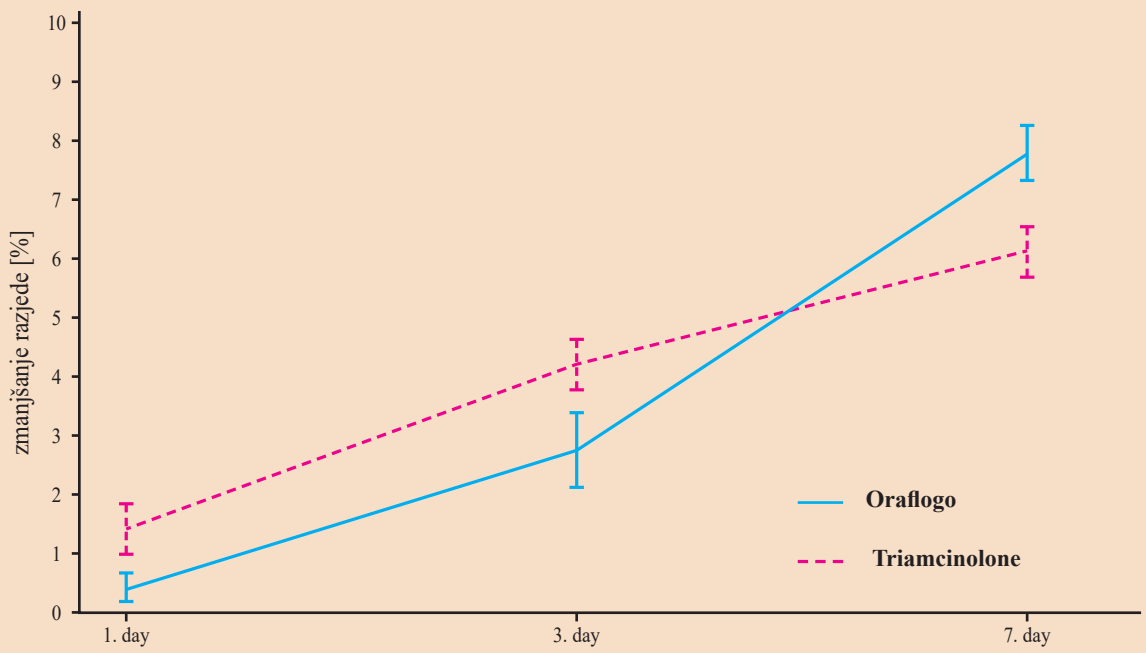
Frequency distribution of pain at end of treatment (7th day). The vertical axis shows the pain scale (VAS); the horizontal axis shows the number of patients.

TABLE 2: REDUCTION IN ULCER PAIN DURING TREATMENT

	1.-2. day	3. day	4. day	5.-6. day	7. day
Oraflogo	7.5±0.5	6.1±0.8	3.6±0.8	2.5±0.7	1.2±0.4
Triamcinolon	6.7±0.4	5.2±0.4	3.7±0.5	2.6±0.7	1.6±0.5

Reduction in ulcer pain during treatment with the two different substances at the measured intervals (1st -7th day) with standard error deviation.

GRAF 6:
COMPARISON OF REDUCTION IN ULCER SIZE DURING TREATMENT



Graphical representation of pain reduction at the start and the consequent time intervals with standard error deviations during the period of research.

Oraflogo and triamcinolone group. A comparison of the differences demonstrated that falls in the level of pain in the Oraflogo group were statistically significantly higher than the falls in pain level in the triamcinolone group (Wilcoxon-Mann-Whitney, p=0,022). This showed that those being treated with Oraflogo gel experienced a larger relative reduction in pain compared to those using triamcinolone.

The comparative study compared the percentage reduction in ulcer size after seven days of treatment. The Wilcoxon rank test rejected the hypothesis (p=0,01) that the percentage reduction would be greater for those using triamcinolone than for those applying Oraflogo. The given hypothesis, which states that triamcinolone is no more effective at reducing ulcer size than Oraflogo, was therefore confirmed. Both treatments, triamcinolone and Oraflogo, are as equally effective in reducing ulcer size.

The comparative study also compared pain reduction as described by patients using the "VAS" scale. With the help of the Wilcoxon rank test, we rejected the hypothesis (p=0,02) which stated that the differences would be less for those using triamcinolone than those using Oraflogo. The smallest difference is 0-10=-10, so this was the best result. The hypothesis was therefore confirmed. Oraflogo and triamcinolone resulted in equal and comparable reduction in ulcer pain during treatment.

Taking into consideration the Bonferroni correction for simultaneous validity of two statistical hypotheses, we are able to confirm the validity of both primary hypotheses with a significance level of 0,05 (p-value of both primary statistics are less than 0,05/2=0,025), namely that hyaluronic acid (Oraflogo gel) is just as effective in reducing ulcer size on the nonkeratinized mucosal surfaces of the mouth, as corticosteroid (triamcinolone acetonide). Likewise, hyaluronic acid (Oraflogo gel) is just as effective in reducing the pain associated with ulcerative lesions on the nonkeratinized mucosal surfaces of the mouth, as corticosteroid (triamcinolone acetonide).

Conclusion

With the aid of statistical tests, both primary hypotheses were confirmed.

By using the Wilcoxon-Mann-Whitney test and Wellek and Hempel (equivalence test), we proved that the comparisons did not show statistically significant differences in pain. The level of pain in both groups was comparable, but it was not possible to statistically prove the differences. The hypothesis was therefore confirmed. Oraflogo gel and triamcinolone led to equal and comparable reductions in ulcer pain during treatment. The Wilcoxon signed-rank test confirmed the hypothesis that both medications, triamcinolone and Oraflogo gel, were equally effective at treating ulcers through reducing their size.

If we take into account the Bonferroni correction for simultaneous validity of two statistical hypotheses, we are able to confirm the validity of both primary hypotheses.

The comparison of differences in the "start minus end value" in the Oraflogo and triamcinolone group revealed that the drops in pain level in the Oraflogo group were statistically significantly higher than the drops in pain levels in the triamcinolone group.

Discussion

Ulcerative lesions are one of the most bothersome benign pathological formations in stomatology. Patients usually complain to their general practitioner or dentist, that the ulcers are very painful or burn, disrupt daily activities and significantly reduce quality of life. Given the expressed discomfort, researchers have tried to limit the pain very early on, to speed up the healing process and reduce the size of the ulcer with various local and systemic treatments.

Brown and Bottomley (1990) were the first to introduce treatment with azathioprine (immunosuppressive) and dexamethasone (corticosteroid), with good results. Miles and colleagues (1993) introduced treatment with triamcinolone acetonide (0,025%) which also achieved good results. This treatment was compared to antiseptic chlorhexidine digluconate (0,12%) but there were no statistically significant differences between the substances.

Similar results were reported by Deshmukh et al. (2014), which prove good statistical significance in the efficacy of triamcinolone acetonide in reducing pain intensity and duration of the ulcerative lesion. They simultaneously exploit the antioxidant, anti-inflammatory and analgesic function of turmeric and prove its comparable efficacy. Romero-Cerecero et al. (2015) demonstrated 89,2% efficacy of triamcinolone (0,1%) in the first seven days of treatment for small ulcerative lesions, which was also proven in our research. The phytopharmaceutical preparation comprised of the tropical therapeutic plant *Ageratina pichinchensis* at a 5% concentration in unpigmented hexane-ethyl acetate extract.

Fani et al. (2012) used phenytoin (medication for cramps, neuropathic pain and arrhythmia) to treat ulcerative lesions in patients with Behcet's disease. Side effects include gingival hyperplasia, connective tissue proliferation (fibroblasts), drowsiness, low blood pressure and bone marrow suppression. It is also dermatotoxic and hepatotoxic. Tests on animals revealed an angiogenic effect and reduced inflammatory response. After seven days, the ulcerative lesions had reduced in size by 53,3% in the group that was being treated with phenytoin, and by 86,7% (p≤0,05) in the group using triamcinolone.

Jacobsen et al. (1997) used thalidomide to treat ulcerative lesions in HIV patients. It is an immunotropic drug which has a sedative effect and it is also a teratogen. Four weeks of treatment led to 55% recovery, compared to only 7% with the placebo. Seven out of twenty-nine patients suffered drowsiness as a side effect and six showed signs of toxicity. Miles et al. (1997) compared pain reduction in the treatment of ulcers with chlorhexidine digluconate (0,12%) and triamcinolone acetonide (0,025%) covered by isobutyl cyanoacrylate and didn't discover any statistically significant differences. It's fair to assume that the covering itself has an influence on pain reduction given that Hunter et al. (1987) didn't find any improvement in the healing of ulcers after six weeks of rinsing with a placebo in comparison to chlorhexidine.

The trend in the research for topical treatment for all types of ulcerative lesions is moving towards natural substances and healing substances without side effects. The authors are trying to overcome the side effects of synthetic corticosteroid hormones, thalidomide, phenytoin and others, by replacing them with chlorhexidine digluconate, turmeric, extracts from the plant *Ageratina pichinchensis* and hyaluronic acid with plant extracts.

Our comparative study focused on the efficacy of treatment of minor ulcerative lesions in the oral cavity by measuring the reduction in size of the ulcerative lesion on the first, third and seventh day after applying triamcinolone acetonide (synthetic corticosteroid) and Oraflogo gel (hyaluronic acid). The polycarbophil protein in the hyaluronic acid adheres to the moist mucosa or lesion which facilitates mechanical protection as it remains on the area applied. It regulates moisture on the surface and facilitates cell transport. Lesions, which have been treated with hyaluronic acid, demonstrate increased cell proliferation, increased angiogenesis and collagen synthesis (Koray et al., 2016).

Our study included participants with fixed prosthodontics. Given the modest number of participants involved in the research, we classified it as a pilot study, even though statistical tests revealed adequate significance and sample credibility. The research produced guidelines which we can make use of in further research. Hereafter, we plan to broaden our research with a larger number of participants and measured parameters. We plan to find out whether fixed prosthodontics significantly affect the response to the given treatment, even though our results related to healing with triamcinolone acetonide are comparable with results from literature, where participants did not have dental prosthetics (Preeti et al. 2011; Fani et al. 2012).

Our research reveals that both substances are statistically significantly effective. On the first and third days of applying the substance to the ulcer, triamcinolone acetonide in orabase was statistically significantly more effective in terms of reducing the size of the ulcer. By the seventh day, the results had changed somewhat and despite the efficacy of both treatments in reducing the ulcerative lesions, the two substances were statistically significantly comparable. In terms of the relative estimation of pain reduction, Oraflogo gel was statistically significantly more effective.

The second variable for which we compared both substances was the reduction in pain. Patients ranked the pain using the visual analogue scale (VAS) from 1 (minimal) to 10 (maximum). In order to determine the reduction in pain we looked at the difference between the value at the start of treatment and value at the end.

The study reveals that the relative drop in pain is statistically significantly higher in the group being treated with Oraflogo gel. Given that other authors (Fani et al. 2012; Miles et al. 1993; Deshmukh and Bagewadi, 2014) describe how treatment for ulcerative lesions with triamcinolone acetonide is successful, we can say that treatment with synthetic corticosteroids, given the associated side effects, can be successfully replaced with the natural substances in Oraflogo gel in the first seven days of treatment.

Summary

Our pilot study confirmed the hypothesis that hyaluronic acid and the additional ingredients (Oraflogo gel) is as effective in treating and reducing the pain associated with minor ulcerative lesions as the proven corticosteroid triamcinolone acetonide in orabase. The level of pain was comparable between both groups yet it wasn't possible to statistically prove the differences. The hypothesis was therefore confirmed and treatment with Oraflogo and triamcinolone had an equal and comparable effect on reducing the pain of ulcers during treatment.

Moreover, a comparison between the differences in "starting minus end value" of pain level in both groups revealed that drops in the levels of pain in the Oraflogo group were statistically significantly larger than those in the triamcinolone group.

The study also confirmed our second hypothesis that the topical application of Oraflogo is just as effective as triamcinolone acetonide in reducing the size of and healing ulcerative lesions. DT

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