

# COMPARATIVE EVALUATION OF TWO FORMS OF DRUGS: PATCH & LOTION OF CLOBETASOL, ON RECOVERY INDICATORS OF APHTHOUS STOMATITIS

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## ABSTRACT

**Aim:** Recurrent aphthous stomatitis is common worldwide that occurs in mouth. Clobetasol as the high potent corticosteroids is available in different preparation such as lotion, pomade, this topical forms are for dermatologic use and according to histological different between skin and oral mucosa, administration of its mucoadhesive dosage form is necessary.

**Materials and Method:** In this study the efficacy of clobetasol patch with advantaged of penetration potential, targeted retention profile and resistance to mechanical factors of saliva and mouth with clobetasol lotion were examined. This study is a one-blinded placebo-controlled. Cases were chosen from patient of school of dentistry. They were randomly divided into four groups. Patients were asked to apply the given agent to the identified ulcer 3 times a day topically. The pain average recorded by VAS scale. The size of ulcer was recorded on examination day and day 5 by examiner. The data were entered to SPSS version 20 and survival analysis and repeated measured ANOVA analysis was performed to compare the pain and recovery time and test analysis was performed to compare the size of the lesion.

**Results:** Between the 4 forms, clobetasol patch has the most effect on treatment of aphthous so that the clobetasol patch on day 2, clobetasol lotion on day 3, placebo patch on day 5 and placebo lotion on day 6 the pain has relief. The lesion size was significantly reduced only in clobetasol patch group.

**Conclusions:** Clobetasol patch is more effective on healing and pain relief than the other topical form that designed for dermatologic used.

**Key Words:** Aphthous stomatitis, Clobetasol, Patch

## Introduction

Aphthous stomatitis is one of the most prevalent oral disease,<sup>1</sup> that diagnosed by single or multiple ulcers, painful and recurrence episodes that is limited to oral cavity.<sup>2</sup> It classified as recurrent and ulcerative oral lesions.<sup>3</sup> According to different studies it affect 10-25% of population. It mostly affect women and children. It could be seen in three different forms:<sup>3</sup>

- small aphthous lesions,
- large aphthous lesions,
- herpetic form aphthous lesions.

Till now, its pathogenesis and etiology is not clear. different etiological factors has been suggested that could be classified in three different group:

1. Immunologic factors such as stress
2. Atrophy or destruction of mucosal layer induced by trauma, nutrition deficiency (such as iron and Vitamin B12)
3. Exposure to antigens like streptococcus mutants, herpes simplex virus and food antigens.<sup>3</sup>

Recent studies suggested that it could be happened because of cytokines dysfunction in oral sub mucosal area. It cause activation of cytotoxic T cells. These cells induce epithelial necrosis and cause clinical symptoms.<sup>3</sup>

Different therapeutic methods like using topical antibacterial agents (chlorhexidine) and topical corticosteroids has been suggested.<sup>3,4</sup> Aphthasol has been proved by FDA as a effective therapeutic agent for aphthous stomatitis treatment.<sup>5</sup> Its mechanism of action has

not been specified yet. it has anti allergic and anti-inflammatory effects.<sup>4</sup>

Corticosteroids that suppress immunologic system consider as first therapeutic line, because activation of cytotoxic T-cells consider as one of the major cause of aphthous stomatitis.<sup>3</sup>

Corticosteroids drugs have different effectiveness, half life and initiation time of action. In order to evaluate effectiveness of Glucocorticoids, their effectiveness would compare with cortisol. According to this classification, drugs such as dexamethasone and betamethasone consider as corticosteroids with the highest effectiveness.<sup>6</sup> The most effective drugs among corticosteroids is clobetasol.<sup>7</sup> Also cortisol considers as the weakest drug in corticosteroid family. According to half-life, corticosteroids divided to three groups:

- short acting that effects less than 12 hours,
- intermediate acting that effects 12-36 hours and
- long acting with more than 36 hours' effectiveness.

Dexamethasone, betamethasone and clobetasol consider as long acting.<sup>6</sup>

Using topical drugs is more effective and more specific than systemic form in order to treat oral mucosa disease. according to studies, topical forms of drugs are more effective and causing less side effects compare to systemic forms.

Topical corticosteroids in different forms like Gel, lotion, cream, ointment and spray are available. Most topical forms of drugs have been designed in order to treat

dermatologic disease. Just a few of such drugs have been designed in order to using in oral cavity.<sup>8</sup>

Penetration capacity of topical drugs is dependent on tissue histological structure including epithelium thickness and amount of keratinization. Histological structure of oral mucosa is different compare to skin, so penetration capacity of drugs on skin and oral mucosa is different. Saliva, chewing and speech are some other factors that influence drug application in oral cavity. The saliva is including different enzymes that influence topical drugs. It is also cause drug dilution and elimination. Drugs also washed out during chewing and speech.<sup>8</sup>

On the other hand, ease of access, vasculature and penetration capacity of oral mucosa, make this area a perfect place for drug delivery.<sup>9</sup>

Drug delivery in oral mucosa needs different formulation and techniques because of histological differences among oral mucosa and skin, different penetration capacity of these tissues and local factor including chewing, speech and saliva in oral cavity. These formulations and techniques called oral mucosa drug delivery. Oral mucosal delivery has the potential of targeted penetration and has the resistance against disturbing conditions like saliva, speech and chewing. Oral lesions need their specific amount of distinct penetration and drug retention profile because of different pathogens, so maximum effectiveness and minimum side effects have achieved.<sup>8</sup>

Different topical corticosteroids like triamcinolone acetonide,<sup>10</sup> fluocinolone acetonide,<sup>11</sup> dexamethasone<sup>12</sup> investigated in aphthous studies. Those studies showed that topical application of those drugs were effective on reduction of aphthous symptoms.

Clobetasol is the most powerful and have the longest half-life. Clobetasol has been used in order to treating aphthous and other oral erosive lesions in those studies.<sup>7</sup>

Rodriguez and Gonzalez in their studies evaluate the clobetasol mouth wash and tooth paste effects on aphthous lesion and gingival erosive lesions. The results indicated that clobetasol is effective in different forms.<sup>13,14</sup>

In 2007 Chuang evaluate clobetasol effects on aphthous lesion in kidney grafts patients using sirolimus. According to results clobetasol directly connected to aphthous lesions cause lesion treatment.<sup>15</sup> Lozada study showed that clobetasol ointment in adhesive paste form was very effective on vesiculo erosive oral lesions.<sup>16</sup>

Available topical forms of clobetasol including cream, lotion and ointments are designed for dermatologic application. Application of ointments and creams in oral cavity is limited, and the most used topical form of clobetasol in oral cavity is lotion form.<sup>8</sup> Absorption rate and effectiveness of lotion form in oral cavity is not investigated yet. Mucoadhesive is one of new methods of drug delivery.

Mucoadhesive is a formulation with ability to adhesion to mucosa surface. Mucoadhesives also called disk, patch or film. It could be composed of different polymers including cellulose or polyacrylate that built by methods like hot melt extrusion or solvent casting. Physical and chemical properties of mucoadhesives influence the bonding and adhesion to the mucosa.<sup>17</sup>

Currently mucoadhesive forms use for drug delivery in nasal, rectum, orbital and oral mucosa. Long and close contact to mucosa that improve drug absorption, protect drug from washing by saliva and mechanical factors like chewing and speech are some of mucoadhesive form advantages.<sup>18</sup>

Different drugs have been designed in the form of mucoadhesive like loratadine for rhinitis allergic and valdecoxib (COX<sub>2</sub> inhibitor) for sub mucosal fibrosis.<sup>19</sup>

Mansour *et al* in 2014 evaluate aloe Vera and myrrh mucoadhesive effectiveness on aphthous lesion. Results indicate effectiveness of both drugs on reduction of aphthous lesion symptoms.<sup>20</sup>

Studies showed that the same drug in different formulations had different therapeutic effects and side effects. Muzio's study in 2008 showed that among topical gel, adhesive denture paste and oral analgesic base, adhesive denture base were the most effective.<sup>21</sup>

Schemer study compared citrus oil mucoadhesive with mouthwash of benzocaine and benzoin tincture on aphthous treatment. Result showed that mucoadhesive is more effective and comfortable.<sup>22</sup>

Kutcher and Meng in their studies founded that mucoadhesive form is more effective than other drugs forms in treatment of aphthous patients.<sup>23</sup>

Prednisolone (low power and short acting) is one of corticosteroids that designed in the form of mucoadhesive. In 2014 Kumria compared mucoadhesive prednisolone with prednisolone suspension. Results showed that mucoadhesive form is more bioavailable than suspension form.<sup>24</sup>

Nano emulsion form of clobetasol propionate has been developed in order to treating dermatological disease. Alam *et al* evaluate this drug effects on psoriasis and atypical dermatitis. They found out that reduction in particle size about 10-20 nm, cause increasing bioavailability and absorption. It also reduce edema compare to placebo group.<sup>25</sup>

In aphthous stomatitis because of sub mucosal inflammation, drug needs to reach this area to be effective. Also remnant of drug, resistance to saliva, chewing and speech is necessary.

The current study evaluates effectiveness of mucosal patch of clobetasol aphthous lesions compare to clobetasol lesion. This form has several advantages including mucosal attachment, close and long duration attachment that improve drug absorption, resistance to washing effects of



saliva and mechanical disturbing factors like chewing and speech.

### Materials and Method

The current study performed as a prospective single blind clinical trial. Sampling was performed by simple non randomized method. Eighty patients have been selected among the whom apply to oral medicine department of Isfahan university of medical science. After explanation of the treatment plan and steps, all patient accepts testimonial.

Included patient in study were 18 – 60 years old, suffering minor aphthous, in first 48 hours after prevalence, the lesion diameter was less than 10 mm and the lesion area were reachable for evaluation and treatment.

The exclusion criteria were including: allergic to clobetasol or a history of severe allergic reaction to other drugs in this family, Major or herpetic form aphtha's, behjet syndrome, using local or systemic corticosteroid in pervious last month, using orthodontics appliance or wire which was in touch with lesion, suffering systemic disease, liver or renal dysfunction, pregnancy or consumption anti pregnancy medication

Patients have gotten a questionnaire that concluded demographic information, medical history. Lesion size was measured by practitioner in first session. Lesion size measured by evaluation the diameter of lesion in area having the maximum diameter. Evaluation performed by periodontal probe. Patient asked to be visited again in 5 days to reevaluate the lesion size.

Selected patients randomly divided into 4 groups, using random numbers table. 2 interventions and 2 testify groups that each groups included 20 patients. Patients in first group had been given a pack of mucoadhesive clobetasol containing 25 pieces (exir danesh asia co , Isfahan , Iran).

Patients were asked to take medications three times a day for 5 days on the lesion site. First dose was applied by practitioner and patient was controlled by practitioner for 30 minutes for probably allergic reactions.

The primary goal of current study was evaluation of pain level (VAS scale) and healing time (days took to patient got 0 score pain) after using four formulations.

Lesion size measured in first and fifth day when patient visited again. In first day, lesion size was measured by periodontal probe in the most diameter of lesion. The size was recorded in questionnaire.

#### Clobetasol mucoadhesive production method:

85 g of methyl cellulose (Sigma & Aldrich, Germany) was added to 2000 CC deionized water (Sigma & Aldrich, Germany). The mentioned combination was mixed by electronic mixer. 50 g of clobetasol (Sigma & Aldrich, Germany) powder was solved in the minimum amount of deionized water. Both solvents were combined and mixed, until a homogenous combinations reach.

after that solvent were dispensed on stainless steel plates in form of drops and was placed in 50°C Owen for 30 minutes to dry. After that patches were cut into proper size and stored. The mucoadhesive were containing 0.05% clobetasol.

Data entered into SPSS software version 20. The ANOVA repeated measures model, kaplan meier and Log rank were used.

### Results

Mean pain score in different groups were analyzed by ANOVA repeated measures model. According to analysis results, there were significant difference among groups. Mean pain score in different groups for each day during treatment period is showed in table 1. In Table 1, values with significant differences (P Value <0.001) marked with different alphabets in each rows.

	Clobetasol Mucoadhesive	Clobetasol Lotion	Placebo Mucoadhesive	Placebo Lotion
Start Day	<sup>a</sup> 4.6 ± 0.13	<sup>a</sup> 4.8 ± 0.16	<sup>a</sup> 5 ± 0.21 <sup>a</sup>	<sup>a</sup> 5 ± 0.19
First Day	<sup>a</sup> 2.8 ± 0.16	<sup>b</sup> 4 ± 0.12	<sup>a</sup> 4.2 ± 0.06 <sup>a</sup>	<sup>a</sup> 4.6 ± 0.19
Second Day	<sup>a</sup> 0.16 ± 0.07	<sup>b</sup> 2.1 ± 0.11	<sup>b</sup> 3 ± 0.15	<sup>a</sup> 4 ± 0.11
Third Day	<sup>a</sup> 0.15 ± 0.01	<sup>b</sup> 0.17 ± 0.09	<sup>a</sup> 2.8 ± 0.17	<sup>a</sup> 3.2 ± 0.16
Forth Day	<sup>a</sup> 0.14 ± 0.03	<sup>a</sup> 0.16 ± 0.09	<sup>b</sup> 1.2 ± 0.05	<sup>a</sup> 2.1 ± 0.03
Fifth Day	<sup>a</sup> 0.13 ± 0.04	<sup>a</sup> 0.13 ± 0.04	<sup>b</sup> 0.17 ± 0.01	<sup>a</sup> 0.8 ± 0.17
Sixth Day	<sup>a</sup> 0.12 ± 0.11	<sup>a</sup> 0.12 ± 0.16	<sup>b</sup> 0.16 ± 0.06 <sup>a</sup>	<sup>b</sup> 0.17 ± 0.12

Table 1: Mean pain level with standard deviation for different groups

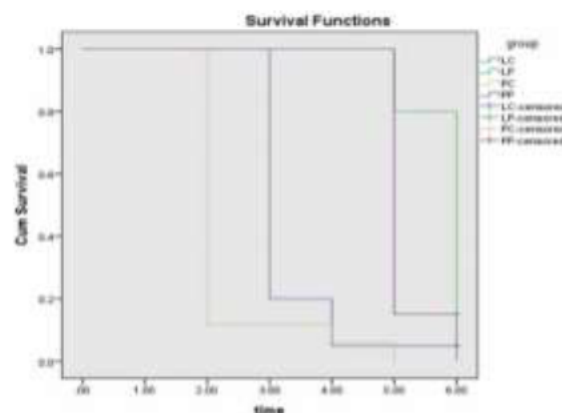


Chart 1: Shows mean healing time (Number of days that take to relive pain) in different groups. the chart 1 also indicate number of healed patients during the time.

In order to compare healing time in four groups, survival method of kaplan meier and Log rank are used. As it is showed in table 2 and chart 1, mean healing time in clobetasol mucoadhesive group was 2 days, in clobetasol lotion group was 3 days, in placebo mucoadhesive group was 5 days and in placebo lotion was 6 days.

Chart 1 shows mean healing time (Number of days that take to relive pain) in different groups. the chart 1 also indicate number of healed patients during the time.

	Median	Mean $\pm$ SD
Clobetazol Lotion	3	3.3 $\pm$ 0.73
Clobetazol Placebo	6	5.8 $\pm$ 0.41
Mucoadhesive Clobetazol	2	2.2 $\pm$ 0.84
Mucoadhesive Placebo	5	5.1 $\pm$ 0.36

Table 2: Median and Mean healing time in different groups

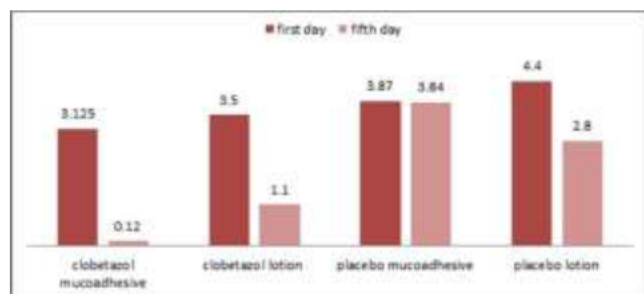


Chart 2: Mean lesion size in first and fifth day (mm).

According to chart 2 values, in clobetasol mucoadhesive and clobetasol lotion groups, mean lesion size was significantly decrease in fifth day compare to first day. In contrast in placebo lotion group lesion size increase in fifth day compare to first day. In placebo mucoadhesive group there is no significant difference among first day and fifth day mean lesion size.

## Discussion

Results showed that mucoadhesive form of clobetasol is more effective on aphthous lesions compare to other groups. In clobetasol mucoadhesive group, patients were free of pain in day 2 (healing time was 2 days). In contrast in clobetasol lotion group, placebo mucoadhesive group and placebo lotion group patients were free of pain and healed in day 3, 5 and 6.

The result showed that mucoadhesive form of clobetasol is more effective than lotion form. (P value<0.001)

Muzzio in 2008 compared effectiveness of different drug forms on healing lichen planus and aphthous symptoms.<sup>21</sup> The results showed that effectiveness of different form of same drug are not same. In that study the most effective form on aphthous lesions were denture adhesive toothpaste.

According to a systematic review which was done in 2010, corticosteroids in different formula and forms had different effectiveness and side effects. For example silico dextrin polymer release corticosteroids better than carboxymethyl cellulose, also clobetasol propionate in adhesive paste form is more effective and has not any side effects.<sup>26</sup>

There is another systematic review which compare different forms of clobetasol like spray, ointment, cream, lotion with the new forms of clobetasol in order to treat psoriasis. The study showed that patients prefer adhesive forms.<sup>11</sup>

Using forms like ointment or lotion in mouth is not suitable for patients because of interfere with saliva and speech. In

order to solve this problem mucoadhesive forms got attention from pharmaceutical companies. Long and close contact to oral mucosa lead to improve drug absorption. Protection against saliva washing effects and other interfering factors like speech are some other benefits. Mucoadhesives are simplify accessibility and increase acceptance for using in chronic disease.<sup>18,27</sup>

Other than mentioned benefits, Kumira in 2014 compared bioavailability of different drug forms. The results showed that bioavailability of mucoadhesive form is more than other forms.<sup>24</sup>

Long and close contact to mucosa lead to improve drug absorption and protect drug from washing by saliva and other interfering factors. Close contact to mucosa lead to improve drug absorption and protect drug from washing by saliva and other interfering factors.<sup>27</sup>

On the other hand, Meng in 2009, studied 216 aphthous patients. Patients treated by mucoadhesive and pill form of aphthasol. Results didn't show any significant differences in efficiency of two forms of drug. also it should kept in mind that patient prefer mucoadhesive form according to results of that study.<sup>23</sup>

Results of current study showed that clobetasol is effective on aphthous lesion. Many studies showed the effectiveness of corticosteroids on healing aphthous lesions. Rodriguez in 2007 evaluated effectiveness of clobetasol oral paste on pain reduction and healing aphthous lesions.<sup>14</sup>

Lozada evaluate effectiveness of clobetasol adhesive paste on vesiculo erosive oral lesions. Results showed effectiveness of this drug.<sup>16</sup>

Gonzalez evaluated effectiveness of 0.05% clobetasol mouthwash on erosive oral lesions. Results improved effectiveness of this drug on symptom reduction of oral erosive lesions.<sup>28</sup>

Also Gonzalez in another study in 2003 found out that combination of clobetasol 0.05% and instating in a Orabase is effective in treating gingival erosive lesions.<sup>13</sup>

Liu evaluated effectiveness of dexamethasone ointments on pain level, lesion size and healing time of aphthous lesions. In that study 120 patients asked to apply dexamethasone ointments 3 times a day after meals for 5 days on the site of lesion. Pain level, lesion size and healing time evaluated after treatment. There was a significant differences between intervention and testify group (P value <0.001).<sup>12</sup>

Some studies suggested that the most effective mechanism of mucoadhesive is their covering effects but results of current study shows that mucoadhesive drug is more effective than placebo muco adhesive (P value <0.001).

In contrast to Mahdi *et al* and Russle and Rodue, results of current study shows that only physical protection of lesion is not enough. Using topical corticosteroids in order to pain reduction and reducing healing time of lesions is more important than covering lesions.<sup>29</sup>



It should be kept in mind that physical protection and covering aphthous lesions by mucoadhesive could help to reduction of aphthous lesions pain. The current study shows that mucoadhesive placebo form is more effective than placebo lotion form on reduction of pain and healing time ( $P$  value  $<0.001$ ). Same results obtained by Kutcher in 2001 that showed mucoadhesive without any drugs could reduce pain in aphthous patients.<sup>30</sup>

### Conclusion

In general, results of current study shows that mucoadhesive form of clobetasol is more effective than clobetasol lotion and placebo. Repeat the current study with more patients that are more homogenous in age and gender is recommended. It also suggested to evaluate probably side effects of clobetasol and effectiveness of combinations of clobetasol and nystatin in mucoadhesive form.

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