

Penicillin in oral aphthosis, new insight for an old drug: A randomized, double-blind, controlled clinical trial

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Background: Oral aphthosis is a painful ulceration of mucus membranes characterized by round or oval lesions with central necrosis and erythematous haloes. Due to unknown etiology, treatment is highly controversial and based mainly on individual experience. The aim of this study was to investigate the safety and efficacy of topical penicillin 6.3.3 for the treatment of recurrent aphthous stomatitis. **Materials and Methods:** This randomized, double-blind, controlled clinical trial was done in Shahid Sadoughi Hospital Clinic in Yazd (2011–2012). Fifty patients aged 15–45 with recurrent oral aphthosis were randomly divided into two groups. After obtaining informed consents, patients in the case and control groups were treated (four times/day for a week), respectively, by topical penicillin 6.3.3 powder and placebo in similar vial. The patients who had acute-onset oral aphthae (≤ 48 h of appearance) with diameter ≥ 5 mm were included. History of sensitivity to β -lactam antibiotics and cephalosporin; spontaneous recovery during < 5 days in previous episodes; concurrent systemic, infectious, or any autoimmune disorders; history of taking drugs (local or systemic) from 2 weeks prior to presentation; alcohol or drug abuse; smoking cigarette or tobacco; and poor compliance were exclusion criteria. Patients were examined in days 0, 3, 6, and 8. The main outcome measure was reduction in the median pain. Burning, pain, erythema, and inflammation were recorded as complications. **Results:** Of 25 patients receiving penicillin, 13 were female and 12 were male. Regarding the pain score (mean difference = 1.6 vs. 0.88, $P = 0.012$) and size of aphthous (mean difference = 9.43 vs. 1.24, $P = 0.008$), patients who received penicillin had significantly better results than the placebo group on day 8 after the treatment. The mean duration to healing was 3 days for penicillin group and 6 days for placebo group ($P = 0.016$). No topical or systemic adverse effects were observed. **Conclusion:** Our study showed a dramatic response to topical penicillin with respect to placebo. Hence, it seems that penicillin could be a safe and effective option in managing oral aphthosis.

Key words: Aphthous stomatitis, penicillin G, treatment outcome

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INTRODUCTION

Oral aphthosis is a painful ulceration of mucus membranes, which is characterized by round or oval necrotic base lesions surrounded by an erythematous margin. They can develop since childhood and usually last 1–4 weeks. The lesions are generally recurrent but are usually self-limited. Usually 10%–20% of the general population is affected during life. Oral aphthosis is classified as major, minor, and herpetiform.^[1] Both the frequency and intensity of the lesions decrease with age.^[2,3]

The exact cause of aphthosis is not clearly understood. Approximately 30% of people who get oral aphthosis have a family history of similar lesions. Human leukocyte antigen alleles such as DR₂, B₁₂, A₁, and A₂ appear to be associated with susceptibility. A small minority of patients have nutritional deficiencies, particularly iron, vitamin B₁₂, or folate deficiency,^[4–6] but the causal relationship is not well established. Oral aphthosis has been reported in celiac disease^[7] or other immune-based conditions such as Behcet's disease^[8] and AIDS (secondary aphthosis).^[9] Local trauma, food allergy, hormonal changes, and emotional factors

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may predispose patients.^[10] Diagnosis is based on clinical findings.^[6] Oral aphthosis may be the first manifestation of connective tissue diseases.^[11]

Oral aphthosis is a disabling condition and is frequently associated with some difficulties in eating, swallowing, and speaking and may affect patient's quality of life. Because the exact etiology of oral aphthosis is unknown, no uniform and standard treatment is proposed for oral aphthosis, and none of the treatment strategies are proved to be completely effective or curative.^[12] Eliminating the risk factors together with Antibacterial/antiviral and immune-modulator agents are frequently used. Such topical remedies such as chlorhexidine, triclosan, tetracycline, minocycline,^[13] mouth washes, topical cephalexin,^[14] sucralfate,^[15] amlexanox,^[16] and glucocorticoids^[17,18] are used with some success. There are several reports about the good response of oral aphthosis to systemic administration of penicillin (PCN). The generally accepted mechanism by which it is postulated to be beneficial could be the antibiotic effect of PCN. On the other hand, some observations support the hypothesis of the anti-inflammatory properties of PCN.^[19,20] Due to the high prevalence of aphthosis in the community and its recurrence, the existing treatment methods have not always been effective. Drug resistant is observed in the clinic. Hence, the high side effects of topical and systemic therapies have led us to seek effective, low-cost, and low-cost topical treatments. In this study, we decided to investigate the efficacy of topical PCN on oral aphthosis.

MATERIALS AND METHODS

Trial design

This randomized, double-blind, controlled clinical trial was done in Shahid Sadoughi Hospital Clinic in Yazd (2011–2012). Fifty patients who had a validated history of oral aphthosis were recruited and randomized to two groups: penicillin or placebo.

Participants

Patients aged 15–45 years who had acute-onset oral aphthae (≤ 48 h of appearance) with diameter ≥ 5 mm in accessible areas such as buccal mucosa, lips, oral bed, and tongue were included in the study. The patients have been informed about the nature and objectives of the study, and all of them signed an informed consent form for participation in the clinical trial.

Patients who had a history of sensitivity to β -lactam antibiotics and cephalosporin; those with spontaneous recovery during < 5 days in previous episodes; those with concurrent systemic, infectious, or any autoimmune disorders; those with a history of taking drugs (local or systemic) from 2 weeks prior to presentation; those with

alcohol or drug abuse; patients smoking cigarette or tobacco; and those with poor compliance were excluded from the study.

Interventions

The first group received PCN 6.3.3 (600,000 IU of benzathine PCN, 300,000 IU of PCN-G potassium, and 300,000 IU of procaine, Zakaria, Tabriz, Iran) and the second group (control group) received placebo. Placebo was in powder form for local use (Fiber clear, Nature Made/Pharmavite, LLC, USA). The patients were asked to apply the powder directed over the ulcer with an applicator, four times a day (1 h after meals and once before sleep). It was recommended to wash their mouths with water before applying the drug, and avoid eating and drinking for an hour and talk less. They were allowed to use acetaminophen (500 mg – 2 g) daily if they had nontolerable pain. Both groups were asked to continue daily treatment for a week.

Outcomes

The groups were compared for lesion size, severity of pain, days to pain cessation, days to ulcer healing, and drug adverse effects in 0, 3, 6, and 8 days after the patients presented to clinics. To assess pain severity and burning, pain-rating-scale was used, the scoring of which is as follows: "0: painless, 1: mild pain, possible to eat well, 2: moderate pain, possible to eat more than half of the meals, 3: severe pain, not possible to eat even half of meals."^[21]

Changes of the ulcer's size during the study were achieved as follows: the maximum and minimum diameters were measured using a caliper graded in millimeters and then surface area index of the ulcer was calculated by multiplying them. Burning, pain, erythema, and inflammation were recorded as complications.

Sample size

Effect of the intervention on the size of the ulcer and the severity of the pain compared to the control group to be statistically significant was considered. With a significant level of 5% and a statistical power of 80%, the minimum sample size was calculated as 25 participants for each group by the formula for "calculating the sample size to compare the average of the two communities." The standard deviation was estimated based on similar studies.^[10]

Randomization

The drug and placebo were prepared and numbered in the same glass according to sterile conditions. Preparations were similar in color, flavor, and other physical properties. The numbering was based on a table of random numbers. After completing the questionnaire and examining the patient, a package containing powder glass, applicator, and a small sterile caliper was delivered to each patient by

the physician with the necessary explanations on how to use the powder.

Blinding

The participants and physician (care provider) were blinded.

Statistical methods

The baseline characteristics were summarized with descriptive statistics. An intent-to-treat analysis was performed. The normal distribution of the data was investigated by Shapiro–Wilk test. The data were analyzed by SPSS 16 (Inc., Chicago, IL, USA), using *t*-test for comparing continuous variables and Fisher's exact test and Mann–Whitney test for comparing group differences between penicillin and placebo. The analysis of covariance (ANCOVA) was used to compare the differences between the groups. The statistical significance level was considered 0.05.

Ethical considerations

The study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Science, Yazd, Iran (number 126962; date 2.12.1389). The study was explained to all respondents willing to participate. All participants had the right to withdraw from the study at any time. Informed consent was obtained from each participant before data collection.

The trial was registered in the Iranian Registry of Clinical Trials (IRCT). The code number of IRCT registration number is IRCT201106102154N2. The trial protocol can be accessed in <https://en.irct.ir/trial/1772>.

RESULTS

Fifty patients accepted to participate and were randomized to one of the treatment groups. There were 25 patients (13 females and 12 males) with a mean age of 29.92 ± 7.48 years in the PCN group. In the placebo group, there were 25 patients (11 females and 14 males) with a mean age of 31.32 ± 8.92 years as well.

Two patients in the PCN group and three patients in the placebo group were excluded from the study due to lack of compliance and discontinuation of the drug [Figure 1].

The mean surface area index was 12.52 ± 15.64 and $11.48 \text{ mm} \pm 15.65 \text{ mm}$ in the PCN and placebo groups, respectively. The mean pain scores were 1.60 ± 0.645 and 1.40 ± 0.816 in the PCN and placebo groups, respectively. The mean age of the first episode of oral aphthosis was 18 years in both groups. Table 1 shows the baseline demographic variables.

By using *t*-test, no statistically significant differences were found in baseline demographic characteristics [Table 1].

Most of the lesions were on lip mucosa (56%). Odynophagia was present in 90% of the patients and discomfort during talking in 40% of the participants.

Pain score was significantly different at the end of the 3rd, 6th, and 8th days between the two groups, and the result was better in the PCN group [Figure 2]. The mean ulcer surface area index decreased significantly after PCN administration [Figure 3]. Our result showed a complete clinical recovery within 3 days of therapy in the PCN group ($P < 0.001$).

A one-way ANCOVA was conducted to compare the effectiveness of two groups. There was a significant difference in the mean pain score on day 3 ($F = 25.7$, $P < 0.0001$) and day 6 ($F = 14.3$, $P < 0.0001$) after treatment. It was statistically significant for size of ulcer on day 3 ($F = 10.27$, $P = 0.002$) and day 6 ($F = 8.8$, $P = 0.005$) after treatment. The mean difference of pain score and size of ulcer were not significant on day 8 after treatment ($P > 0.05$).

The mean days to improvement in the PCN group was 2.79 days in oral ulcer with age ≤ 24 h; in the placebo group, this item was 5.9 days [Table 2].

In this study, three patients (12%) just complained of minor burning sensation after application of drug, which was not significantly different in comparison with placebo. No other systemic or local side effects were reported. There was no significant complication in each group.

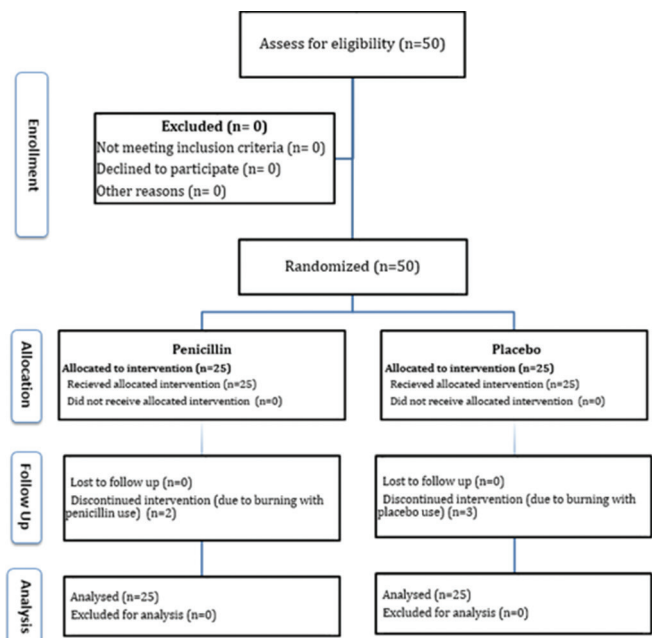
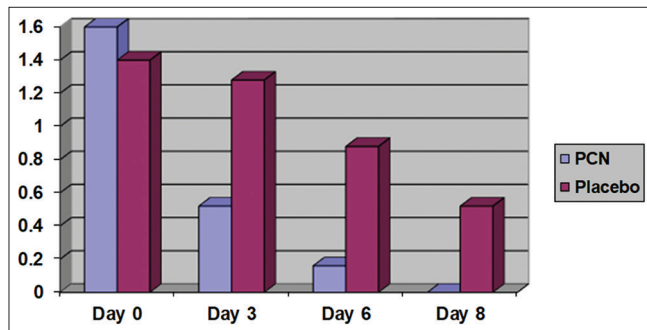
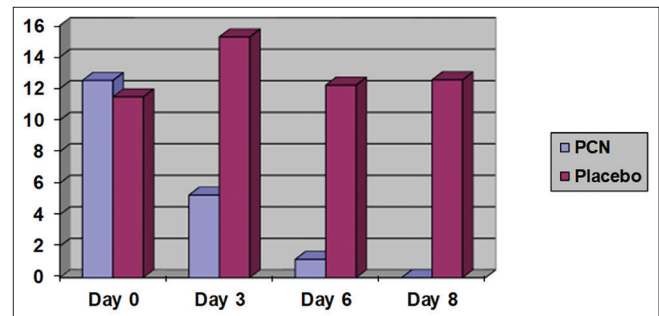


Figure 1: Flow diagram, demonstrating random allocation of patients into intervention and control groups, along the course of study

Table 1: Baseline characteristics of the studied population

Baseline findings	Penicillin (n=25)	Placebo (n=25)	P
Number (male/female)	12/13	14/11	0.395
Mean age, years (range)	29.92 (15-45)	31.32 (15-45)	1.551
Mean initial ulcer size±SD (mm ²)	12.52±15.46	11.48±15.65	0.747
Mean initial pain score±SD	1.60±0.645	1.40±0.816	0.270
Mean age at first ulcer±SD	18.60±6.87	18.44±4.8	0.925
Mean of recurrence (per year)±SD	6.84±3.48	8.44±4.02	0.139
Mean of healing time			
With treatment in previous episode (days)±SD	11.44±3.69	9.76±3.97	0.128
Without treatment in previous episode (days)±SD	13.64±13.01	19.88±20.43	0.204
Time of onset of ulcer, n (%)			
<24 h	15 (60)	14 (56)	0.770
>24 h	10 (40)	11 (44)	0.770
Location			
Tongue/floor of mouth, n (%)	3 (12)	4 (16)	0.830
Buccal mucosa, n (%)	8 (32)	9 (36)	0.830
Lip number (%)	14 (56)	12 (48)	0.830

SD=Standard deviation

**Figure 2:** Mean of pain score among penicillin and placebo groups**Figure 3:** Mean of ulcer size among penicillin and placebo groups

DISCUSSION

Our study showed a dramatic response of oral aphthosis to topical PCN with respect to placebo. This effect was obvious not only for pain relief but also for the healing rate. The rationale for the use of topical agents in case of a topical lesion is an acceptable strategy. Although some of the oral aphthae are associated with hidden or overt systemic lesions, because the etiology of the disease is not completely understood, and none of the present remedies are curative, finding a topical agent with favorable response could be a therapeutic goal in aphthosis. The mechanism of action of PCN in oral aphthosis remains to be elucidated, but we presume that the anti-inflammatory properties of PCN could have a critical role in rapid ulcer healing in oral aphthosis. This dramatic response could be seen after topical or systemic administration of glucocorticoids or colchicine in the case of oral aphthosis. This observation supports the immunologic rather than the antimicrobial basis for this phenomenon.

In our recent trials, we observed a dramatic response to administration of systemic PCN in several cases of

autoimmune disorders.^[22] However, the story comes to be more complicated when several investigators tried to confirm the microbial nature of oral aphthae; Barile *et al.* isolated L-form of Streptococci from 93% of oral aphthae.^[21] Changes in the microbial flora of the mouth are effective in causing aphthosis.^[23] On the other hand, a plenty of studies indicated inflammatory and immunologic basis for oral aphthosis. Some of them postulated that abnormal immune response to oral microbial flora may be the cause. Hence, considering the dual pathophysiologic nature of oral aphthosis, it seems that the magic effects of PCN in oral aphthosis could be attributable to a bimodal (antibiotic and anti-inflammatory) therapeutic effect of PCN.^[24-26]

Brook *et al.* showed that benzathine PCN plays its anti-inflammatory role via conjugation with interleukin (IL) IL-1B, IL-2, IL-5, and IL-13. Other studies also support the immunomodulatory effects of PCN.^[27,28] Tumor necrosis factor- α and IL-6 and IL-17 are raised in recurrent aphthous.^[29] Kiraz *et al.* reported the clinical response of mucocutaneous lesions in Behcet's disease to intramuscular PCN administration.^[30] Al-Waize *et al.* proved that adding colchicine to intramuscular PCN can significantly improve

Table 2: Association of ulcer age and time to improvement in two groups

Group intervention ulcer age	n	Mean days to improvement	P
Penicillin (h)			
≤24 h	14	2.79	0.163
>24 h	9	3.56	
Placebo			
≤24 h	12	5.9	0.929
>24 h	11	5.86	

clinical response.^[31] Kerr *et al.* were the first group of scientists who published an article on topical (troche) PCN in oral aphthosis, and the authors also emphasized on its anti-inflammatory action. However, fewer studies followed this important finding. Zhou *et al.* also showed that potassium PCN G is safely effective in oral aphthosis.^[32]

Our trial had the advantage of using a unique form of worldwide available PCN (6-3-3), which consists of 600,000 IU of benzathine PCN, 300,000 IU of PCN-G potassium, and 300,000 IU of procaine PCN, which favorably dresses the oral ulcers. Hence, the anesthetic properties of built-in procaine may intensify therapeutic profile in clinical use while they have no documented effect on ulcer healing. The only adverse reaction of topical powder of PCN was negligible (mild burning sensation on topical application in three cases) and was comparable to mild local symptoms in the placebo group. The frequency of local adverse effects in Kerr's study was remarkable and was observed in about 65% of patients compared to 12% in our study. This difference in frequency can be attributable to the adherent analgesic effect of procaine, which makes PCN 6-3-3 more advantageous than PCN troches used by Kerr's. Healing time (the time from topical application to clinical improvement) was remarkably shorter than the previous remedies ($P < 0.001$). This issue was less addressed in similar studies. We notice that this method of treatment could be limited to a few number of oral aphthae which are in good access of applicator and not advised in multiple diffuse oral aphthosis invading posterior parts of the mouth. In these situations, the knowledge of PCN mouth washes could become into consideration in future.

Our *post hoc* observations showed less frequent oral aphthous recurrence in patients who received topical PCN, and it could be due to the dual therapeutic effects of PCN in oral aphthosis. However, these data need more and better designed studies in future. In a pilot unpublished study, we tried parenteral PCN in several cases of rheumatic diseases including rheumatoid arthritis, Behcet's disease, systemic sclerosis (with prominent fingertip ulcer and Raynaud's phenomenon), and some cases of erythema nodosum and idiopathic uveitis with dramatic responses in most instances.

All these data support more and more the possibility of the powerful anti-inflammatory rather than antibiotic effects of PCN. The effect of penicillin in the treatment of aphthous has been reported.^[33,34] We conceptualized that using troches is not applicable and convenient to most of the oral aphthous and PCN powder could be easily available to damaged tissues without interfering speech and swallowing.

Limitations

We had some limitations in covering all patients with primary and systemic aphthous and oral aphthous in pediatric age group, but it seems that due to similar pathophysiologic and pathologic nature of oral aphthosis, this method of treatment would be effective in selected patients with secondary aphthosis and pediatric cases as well. Long-term follow-up of treated patients in a larger sample size may clarify the possible role of PCN in preventing recurrent and refractory oral aphthosis. It was best done in several clinics.

CONCLUSION

Participants using penicillin reported lower pain levels, smaller ulcer size, and earlier recovery after treatment, whereas participants did not show improvement in these variables by taking placebo. The difference between the two groups was significant except for the ulcer site and the time of refer. Therefore, due to the low side effects and significant improvement in symptoms in this clinical trial, we recommend topical penicillin powder as the first choice drug for treatment, which is in good access of applicator and not invading the posterior parts of the mouth. Although it is necessary to consider the effect of other drugs in the treatment of patients or as adjuvant drugs by further studies.

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Conflicts of interest

There are no conflicts of interest.

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