TREATMENT OF RECURRENT APHTHOUS STOMATITIS WITH SYSTEMIC ZINC SULFATE

NACI M. BOR
AYVAZ KARABIYIKOGLU
TÜRKAN KARABIYIKOGLU

SUMMARY: A series of 67 out-patients with recurrent aphthous stomatitis with respect to zinc and copper deficiency were studied at the Medical and Surgical Research Center of Hacettepe University Medical School. Before the treatment serum zinc and copper deficiencies were observed in 54 cases of the entire series. Of these 40 patients were deficient in serum Zn only (mean 75.44 ± 9.55 μg/dl), 2 cases serum Cu (mean 80 μg/dl) and the remaining 12 were deficient in both trace metals (74.91 ± 8.60 and 78.36 ± 7.14 respectively). The remaining 15 patients revealed normal values for these two trace metals at the first evaluation. Following one, two and three months of treatment serum Zn (93.37 ± 13.49, 92.87 ± 14.88 and 98.94 ± 16.06) and Cu (89.45 ± 14.97, 97.82 ± 15.86 and 95.45 ± 8.49) levels of the patients rose parallel to the improvement in clinical findings. Of the 67 patients on systemic Zinc sulfate and copper sulfate treatment 40 revealed complete recovery of ulceration, and twenty-two showed definite improvement after 3 months of treatment. In the remaining 5 recurrences were observed, lesions however, were of shorter duration, painless, and smaller in size. The statistical analyses of the results were made using paired-t test.

Key Words: Recurrent aphthous stomatitis, zinc sulfate, copper sulfate, serum Zn, serum Cu, Zn of 10^{10} erythrocytes.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is one of the most common diseases affecting the oral mucous membranes. They are painful, recurrent, usually small (2-4mm), round or ovoid, single or multiple necrotizing ulcerations. Approximately 20 percent of the general population will have these peculier ulcerations during a period of his life (1-9).

The literature is replete with reviews, clinical and experimental studies directed toward elecudation of the etiology and pathogenesis of RAS. These may be conveniently divided into host factors-genetics, nutrition, gastrointestinal diseases, hormones, and psychological and environmental factors, infection, trauma, allergy and cigarette smoking (1, 5, 6, 8-13). This long list clearly indicates that the primary cause has as yet not been established. Although many modalities of treatment have been advocated, a truly effective therapeutic regimen to prevent RAS is not yet available (1, 3, 4, 7). Additional research on the aetiology, pathogenesis and treatment of RAS is needed (1). We therefore conducted this study designated to establish the efficiacy of systemic zinc sulfate and copper sulfate in patients with recurrent aphthous stomatitis.

MATERIALS AND METHODS

Sixty-seven out patients with recurrent aphthous stomatitis between ages 4 and 75 (mean age, 32.8 years) referred to the medical and surgical research center of Hacettepe University were included in this study. 37 of these patients were male (mean age, 29.5 years), and 30 were female (mean age, 32.5 years). They had suffered from their ulcers since between 2 months and 30 years (mean, 4.4 years) and activity periods of individual ulcers ranged between 5 to 30 (mean 10.3) days. The ulcers were usually multiple in number and localized mainly on the tongue and lips. All of he patients complained of severe pain.

*From Medical and Surgical Research Center, Faculty of Medicine and Oral Diagnosis and Radiology, Faculty of Dentistry, University of Hacettepe, Ankara, Türkiye.

The diagnosis of RAS was made by detailed history and clinical examination of the oral ulcers. 35 of 67 patients complained only from recurrent aphthous stomatitis. The remaining 24 of the 32 patients had some form of alopecia, 7 patients had acne vulgaris, 2 patients had allergy, and the last 2 patients had migren associated with RAS. The onset, distribution, number, duraion of ulcers, and existance as well as severity of localized pain were recorded in all patients. Cases with bullae, history of trauma acute ulcerative gingivitis, herpes simplex, and Reiter's syndrome, Behcet's syndrome, and gastrointestinal or endocrine system disorders were excluded. None of the patients were taking any other medications during the time they remained under this specified therapy.

A venous blood sample was taken from each of the patients after a night's fasting before starting treatment. Serum Zn, Cu levels, and Zn contents of 10^{10} erythrocytes were measured using atomic absorption spectrophotometer (Perkin-Elmer Model 103) (14). Routine blood and urine analyses were done.

Clinical and hematological controls were repeated every month. Changes in the number and durations of oral ulcers and the severity of the pain were noted. Pretreatment period of each patient acted as his or her own control.

According to the results of monthly determinations of thee trace metals all the patients were given 50-200 mg of $ZnSO_4.7H_2O$ molecule once or twice and 0-5 mg o $CuSO_4.5H_2O$ molecule per day orally during or after meals.

Improvement was considered to be reduction in frequency, size, numbers, and duration of ulcers for the individual patients. Each of these parameters were subdivided as complete recovery, definite improvement or recurrence.

The results before and after the treatment were evaluated statistically.

RESULTS

Clinical findings

Before the treatment, the patients had usually one or two attacks per month. During the first month following the treatment a reduction in the number of ulcers and shortening of the activity periods were observed. They were less painful and smaller in size.

The patients however felt a subjective relief during the first month and an objective improvement was observed after 3 months of treatment. Of the 67 patients on systemic $ZnSO_4$ and $CuSO_4$ treatment of 3 months duration 40 (59.7%) revealed complete recovery of ulceration, and 22 (32.8%) definitive improvement. In the remaining 5 (7.5%) recurrences were observed. These recurrent lesions, however, were also of shorter duration, smaller in size, painless, and the periods between the episodes were significantly prolonged.

Serum Zinc and Copper levels, and zinc contents of 10^{10} erythrocytes:

Before treatment, serum Zn and Cu deficiencies were observed in 54 (86.59%) of 67 patients with RAS. Of these, 40 were deficient in serum Zinc only, 2 in serum copper, and the remaining 12 patients were deficient in both trace metals.

The patients were divided into 3 groups according to initial serum Zn and Cu levels. Group 1. Consisted of 13 (19.4%) patients whose serum Zn and copper levels were within normal values.

In this group, 8 patients were male and 5 were female. Their ages ranged from 15 to 46 years (mean 34.1 years). The patients had aphthae for periods ranging 2 months to 6 years (mean 3.3 years) and activity periods of individual ulcers were between 5 to 30 (mean 10.3) days. Minor ulcers were seen in 90% of patients.

The mean Zn levels of these 13 patients were 105.33 $\pm$17.58, 104.22 $\pm$ 27.50 and 111.78 $\pm$ 19.86 μg/dl one, two and three months after treatment respectively (Table 1). Of these 13 patients, 8 showed complete remission of ulcers and in addition 5 cases improved before the 3rd month of treatment. No evidence of recurrence were encountered in this group.

Before treatment, the mean Cu level of the first group was 102.44$\pm$14.41 μg/dl, and (95.33$\pm$14.80, 97.33$\pm$10.34 and 95.78$\pm$9.40 μg/dl) one, two and three months after treatment respectively (Table 2).

The differences between pre-treatment and of monthly evaluations following treatment in mean serum Zn, Cu levels and Zn contents of 10^{10} erythrocytes were not statistically significant ($p > 0.05$).

Group 2. Consisted of 12 patients whose serum Zn and copper levels both were below normal values. The

Table 1: Serum Zinc Levels (mean μg/dl $\pm$ SD)

	First group n: 13	Second group n: 12	Third group n: 40
Before treatment	97.33 $\pm$ 6.08	74.91 $\pm$ 8.60	75.44 $\pm$ 9.55
1st month after treatment	105.33 $\pm$ 17.58	88.18 $\pm$ 14.90	93.37 $\pm$ 13.49*
2nd month after treatment	104.22 $\pm$ 27.50	89.27 $\pm$ 12.63*	92.87 $\pm$ 14.88*
3rd month after treatment	111.78 $\pm$ 19.86	90.73 $\pm$ 8.78*	98.94 $\pm$ 16.06*

Table 2: Serum Copper Levels (mean μg/dl ± SD)

	First group n: 13	Second group n: 12	Third group n: 40
Before treatment	102.44 ± 14.41	78.36 ± 7.14	111.44 ± 25.38
1st month after treatment	95.33 ± 14.80	89.45 ± 14.97*	105.75 ± 30.45
2nd month after treatment	97.33 ± 10.34	97.82 ± 15.86*	109.19 ± 27.40
3rd month after treatment	95.78 ± 9.40	95.45 ± 8.49*	112.06 ± 28.09

ages of the patients ranged from 22 to 75 years (mean 34), 6 were female and 6 were male. The aphthae had been present for periods of 4 to 17 years (mean 9.3), and activity periods of individual ulcers were between 7 to 30 (mean 12.7) days. 6 of these 12 patients had complete remission of ulcers. In addition 5 cases were improved. Only one patient had recurrence after the 3rd month of treatment.

Before treatment the mean serum zinc level in this group was found to be 74.91±8.60 μg/dl. Following the first month of treatment, serum Zn levels began to rise and the mean serum Zn levels were (88.18±14.90, 89.27± 12.63 and 90.73±8.78 μg/dl) at the end of one, two and three months respectively (Table 1). The mean serum copper level 78.36±7.14 μg/dl before treatment. The mean levels were found to be (89.45±14.97, 97.82± 15.86 and 95.45±8.49 μg/dl) one, two and three months after treatment respectively (Table 2).

The differences between pre-treatment and 2nd and 3rd months following treatment in mean serum Zn levels, and Zn contents of 10^{10} erythrocytes, and pre-treatment and of monthly evaluations following treatment in mean serum Cu levels were found statistically significant ($p<0.05$).

Group 3. Consisted of 40 (59.7%) patients whose serum Zn levels were below normal values, their serum Cu levels however, were within the normal range. In this group 22 cases were male and 18 were female. Their ages ranged from 4 to 51 years (mean 30.3). These patients had aphthae for periods ranging 3 months to 30 years (mean 9.5 years) and activity periods of individual ulcers were between 7 to 30 (mean 18.8) days.

Before treatment, the mean serum Zn level was 75.44 ±9.55 μg/dl and was observed to rise to (93.37±13.49, 92.87±14.88 and 98.94±16.06 μg/dl) in one, two and three months of treatment respectively (Table 1).

Of these 40 patients, 24 revealed complete remission of ulcers. In addition 12 cases improved and the remaining 4 patients observed recurrences after 3 months of treatment. Each of these last patients however were somewhat better with less pain, shorter duration and longer periods of remission.

Of the total series of 67 patients only 2 had low serum Cu levels. Before treatment the mean serum copper level of each of these 2 patients was 80 μg/dl, and (mean 89, 90 and 91 μg/dl) following the treatment respectively. They responded favorably to treatment (Table 2).

Before and after treatment Zn contents of 10^{10} erythrocytes in all 3 groups were within normal values. These values were found to be (11.98±2.27, 12.20±1.68, 12.62±2.24 and 13.07±3.02) in 1st group, (12.02±2.11, 12.87±1.62, 13.11±2.23 and 13.79±2.41 in 2nd group, and (11.40±2.15, 12.49±2.10, 13.05±2.21 and 13.06± 2.30 μg) in 3rd group respectively (Table 3).

The differences between pre-treatment and of each month following treatment in mean serum Zn levels and Zn contents of 10^{10} erythrocytes were statistically significant ($p<0.05$), however in mean serum Cu levels were not significant ($p>0.05$).

DISCUSSION

Recurrent aphthous stomatitis patients are frequently seen in everday dental practice (1, 3). Its cause is unknown and the proposed methods are numerous, yet

Table 3: Zn Contents of 10^{10} erythrocytes (mean μg/dl ± SD)

	First group n: 13	Second group n: 12	Third group n: 40
Before treatment	11.98 ± 2.27	12.02 ± 2.11	11.44 ± 2.05
1st month after treatment	12.20 ± 1.68	12.87 ± 1.62	12.49 ± 2.10*
2nd month after treatment	12.62 ± 2.24	13.11 ± 2.23*	13.05 ± 2.21*
3rd month after treatment	13.07 ± 3.02	13.79 ± 2.41*	13.06 ± 2.30*

no definitive therapy is available. In the absence of a complete understanding of the etiology of the disease treatment remains symptomatic and no cure is attained despite the fact that many topical and systemic medications have been proposed and utilized (1,3,4,15,16).

Previous reports indicate that systemic zinc treatment causes an improvement or remission in selected patient with RAS (17, 18). Among these Battistone and associates (17, 19), McCray and co-workers (17, 20), and Mesrobian and Shklar (17, 21) have shown improvement in oral wound healing rates in hamster and guineapigs following administration of zinc sulfate or zinc cysteamine-N-acetic acid.

Merchant and associates have reported a marked reduction in number of ulcers and of their sizes, activity periods and especially of pain usually a total of 660 mg of Zinc sulfate per day in a series of 32 patients with recurrent aphthous ulceration. They suggested that RAU may be due to several causes, one of which may be local or general deficiency of zinc or a defect in its metabolism, perhaps at the cellular level (17). In their series, the most notable improvement was a reduction in the recurrence rate. Seventeen patients, 8 with initial serum zinc level above 110 μg/dl and 9 below, were provided zinc sulfate supplementation up to a total of 660 mg/day. All patients with initial serum zinc levels <110 μg/dl showed improvement. Three reported complete remission with however recurrences few weeks after sessation of treatment (17). Serum copper levels of these patients were not reported.

Wray and his group observed no therapeutic effects with systemic zinc sulfate over a 3-month period in a double-blind crossover trial involving 20 patients. Their lack of success was considered secondary to selection of patients whose pre-treatment serum zinc levels were not reduced. They apparently did not measure their zinc levels while under therapy (22).

In this study, 67 patients with RAS were followed up with monthly controls to determine their response to systemic zinc sulfate treatment.

Before treatment, serum Zn levels in 40 patients, serum Cu levels in 2 patients and both of these trace metals in 2 patients were found below normal values. Oral zinc treatment using 50-200 mg of zinc sulfate three times daily appeared to alleviate the symptoms in a great majority of our patients as documented by healing or reduction in the size and number of the ulcers and their activity periods. The most notable improvement was disappearance of pain in all patients.

The clinical and hematological results of treatment were very good in a follow-up period of 3 months. Of the 67 patients 40 revealed complete remission of the disease, and 22 showed definitive improvement. In the remaining 5 patients who still had recurrences while under treatment over a 3-month period, the lesions were however of shorter duration, smaller in size and separated with wider periods of time free from complaints. It should also be stressed here that in patients with reduced serum Zn levels the clinical improvement occurred simultaneously with the return of reduced Zinc levels to normal.

As observed in Tables 2 and 3 zinc deficiency shows a closer correlation with development of aphthous stomatitis. Further consideration of these tables discloses that return of serum and erythrocyte zinc levels towards normal is followed by disappearance of RAS in almost all cases.

Discontinuation of the drug was followed by recurrence of the symptoms in almost all cases early in the course of therapy. This was correct for some cases even after months of oral zinc supplementation. This response was therefore utilized as a method of control for the influence of zinc sulfate treatment and it obviated further control studies for its influence.

Since zinc deficiency was observed in all of these patients it is easy to understand the reason for oral zinc administration. However, the same can not be told for copper supplementation. It is interesting from this respect that copper even though may be at normal levels before treatment, it is frequently reduced following a few days of oral zinc treatment. What is more interesting is the observation that following institution of copper deficiency the original symptoms may recur or become aggravated. In order to prevent this we adopted the method of routine copper supplementation in small doses of patients from the beginning of oral zinc therapy. In innumerable instances we have been able to prevent development of copper deficiency while we restore serum zinc levels to normal (23-26). It is important to note here that in no case any sign of copper toxicity developed. Because of the monthly controls serum copper level never reached toxic levels.

An interesting consideration is whether copper deficiency alone may also lead to development of apthous ulcerations of the mouth. No definite answer could at present be given to this important question. We are presently considering the possibility of other trace elements playing a role in the ethiopathogenesis of this unique disorder. It is furthermore observed that in most of our cases serum copper levels were within normal values at the beginning of the treatment. In five cases they were somewhat reduced. It is important to note as the patients responded to treatment with zinc and copper levels in serum both returned to normal. Simultaneously the patients improved clinically.

REFERENCES

1. Antoon JW, Miller RL : Aphthous ulcers-a review of the literature on etiology, pathogenesis, diagnosis, and treatment. JADA 102:803-807, 1980.

2. Scully C, Yap PL, Boyle P : IgE and IgD concentrations in patient with recurrent apthous stomatitis. Arch Dermatol, 119:31-34, 1983.

3. Poswillo D, Partridge M : Management of recurrent aphthous ulcers. Br Dent J, 157:55-57, 1984.

4. Schulkind ML, Heim LR, South MA, Jeter WS, Small PA : A case report of the successful treatment of recurrent apthous stomatitis with some preparations of orally administered transfer factor. Cell Immunol, 84:415-421, 1984.

5. Eversole LR, Shopper TP, Chambers DW : Effects of suspected foodstuff challenging agents in the etiology of recurrent apthous stomatitis. Oral Surg, 54:33-38, 1982.

6. Rennie JS, Reade PC, Scully C : Recurrent apthous stomatitis. Br Dent J, 159:361-367, 1985.

7. Graykowski EA, Barile MF, Lee WB, Stanley HR : Recurrent apthous stomatitis. JAMA, 198:129-136, 1966.

8. Maurice M, Mikhail W, Aziz M, Barsoum M : Aetiology of recurrent apthous ulcers (RAU). J laryn Otol, 101:917-920, 1987.

9. Hay KD, Reade PC : The use of an elimination diet in the treatment of recurrent apthous ulceration of orally cavity. Oral Surg, 57:504-507, 1984.

10. Correl RW, Wescott WB, Jensen JL : Recurring, painful oral ulcers. JADA, 103:497-498, 1981.

11. Peavy DL, Nelms DC, Mackler BF : Failure of autologous oral epitelia to activate RAS lymphocytes. Clin Immunol Immunopathol, 22:291-295, 1982.

12. Mundy TM, Miller JJ : Behcet's disease presenting as chronic apthous stomatitis in a child. Pediatrics, 62:205-208, 1978.

13. Graykowski EA, Drimnan A, Gier R, et al : Treatment of recurrent apthous ulcerations. J Oral Path, 7:439-440, 1978.

14. Parker MM, Humoller FL, Mahler DJ : Determination of copper and Zinc in biological materials. Clin Chem, 13:41-48, 1967.

15. Wray D, Ferguson MM, Mason DK, et al : Recurrent aphthae: treatment with Vitamin B_{12}, folic acid and iron. Br Med J, 2:490-493, 1975.

16. Wray D, Ferguson MM, Hutcheon AW, Dagg JH : Nutritional deficiencies in recurrent aphthae. J Oral Pathol, 7:418-423, 1978.

17. Merchant HW, Gangarosa LP, Glassmann AB, Sobel RE : Zinc sulfate supplementation for treatment of recurring oral ulcers. South Med J, 70:559-561, 1977.

18. Merchant HW, Gangarosa LP, Morse PK, STrain WH, Baisden CR : Zinc sulfate as a preventive of recurrent apthous ulccers. J Dent Res, 60A:609-611, 1981.

19. Battistone GC, Rubin MI, Cutright DE, et al : Zinc and bone healing: effect of zinc cysteamine-N-acetic acid on the healing of experimentally injured guinea pig bone. Oral Surg 34:542-552, 1972.

20. McCray LA, Higa LH, Soni NN : The effect of orally administered zinc sulfate on extraction wound healing in hamsters. Oral Surg, 33:314-322, 1972.

21. Mesrobian AZ, Shklar G : The effect of dietary zinc sulfate supplements on the healing of experimental extraction wounds. Oral Surg, 28:259-265, 1969.

22. Wray D : A double-blind trial of systemic zinc sulfate in recurrent apthous stomatitis. Oral Surg, 53:469-472, 1982.

23. Bor NM : Copper supplementation in treatment of zinc deficiency disease. JIASci, 2:5-6, 1989.

24. Bor NM, Öner G, Sezer V, Özkaragöz K : Zinc and copper deficiency in patients with allergic diseases and treatment with zinc sulfate. New 1st Contr Clin Sci, 13:58-59, 1980.

25. Bor NM, Karabiyikoglu A, Dereagzi H : Trace metals in treatment of psoriasis. JIASci, 2:226-229, 1989.

26. Bor NM, Karabiyikoglu A, Karabiyikoglu T : Zinc sulfate in treatment of the patients with recurrent apthous stomatitis. JIASci, 3:70-73, 1990.

Correspondence:
Naci M. Bor
Hacettepe Universitesi
Tip Fakültesi
Tibbi ve Cerrahi Arastirma Merkezi
Ankara, TÜRKIYE