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ORAL ZINC IN ACNE VULGARIS: A CLINICAL AND METHODOLOGICAL STUDY

Kerstin Göransson,[1] Sture Lidén[1] and Lars Odsell[2]

[1]*Department of Dermatology, University of Umeå, Sweden and* [2]*AB Draco, Dermatological Group, Lund, Sweden*

Abstract. In a double-blind investigation of 54 patients suffering from acne vulgaris, the effect of 0.6 g of oral zinc sulphate daily versus placebo was studied. During the active treatment period of 6 weeks, the acne improved by about one-third, as rated with a score system. Clinical comparison with placebo showed the result of zinc sulphate therapy to be slightly, but statistically significantly better. Various methods for the clinical evaluation of acne were studied. Counting of acne lesions was found to be a more precise method than assessment according to the opinion of the patients and the assessment of colour photographs. The correlation between the results obtained by lesion counting and evaluation by photographs was low, as was also the reproducibility of photographic assessment.

Key words: Acne vulgaris; Oral zinc treatment; Methods for clinical assessment

Antibiotics have been in use for more than 25 years in the treatment of acne. Without doubt, this treatment has been a real advance, especially for the more extensive types of the disease. For obvious reasons the prolonged use of antibiotics, mainly tetracyclines, even in low doses, is looked upon with suspicion by all concerned. An alternative to this type of treatment would thus be of definite value.

In recent studies Michaëlsson et al. (2, 3) reported on very good results in acne treatment with the use of oral zinc sulphate. The aim of the present study was to make an independent study of the effects of this treatment and also to evaluate the most commonly used methods of assessing the effect of acne treatment.

MATERIAL AND METHODS

The trial was performed between the beginning of October 1974 and the end of January 1976. The trial was divided into two parts, leaving an interval from May to September 1975, when natural ultraviolet radiation might otherwise have interfered with the results.

59 out-patients with acne, of grades 1–3 according to the Pillsbury classification, entered the trial after giving their informed consent. The patients were allocated to either of the two treatments in accordance with a randomized administration scheme. 29 patients were allocated to zinc sulphate treatment and 30 patients to placebo.

5 patients did not complete the trial. In the zinc treatment group one patient dropped out because of exacerbated acne during the first weeks of treatment. Another patient in this group and 3 patients in the placebo group dropped out for non-medical reasons. In the zinc group 8 women and 19 men, with a mean age of 19.5 (range 14–38) years and in the placebo group 14 women and 13 men, with a mean age of 21.1 (range 16–30) years completed the study.

The patients were given three effervescent tablets each day for 6 weeks, containing either zinc sulphate 0.2 g, corresponding to 45 mg Zn^{2+} (Solvezink®, AB Tika, Sweden; a subsidiary of AB Astra, Sweden), or placebo. The tablets were identical regarding shape, taste, and colour. Both doctors and patients were kept in ignorance as to which tablets were active and which were not.

No simultaneous acne medication was allowed during the trial, and to enter the trial the patients should not have been medically treated for a period of at least 4 weeks prior to the test.

Each patient included in the final material was examined three times by the same investigator (K. G.); before treatment, after 3 weeks of treatment, and after 6 weeks of treatment. On every occasion the investigator counted the different acne lesions on the patient's face according to the lesion definitions shown in Table I. The facial region was defined as the area limited by the scalp and the mandibular edge. No lesions were counted on the back or on the neck. To make possible an overall estimation of the severity of the individual patient's acne, each type of lesion was given a severity index (see Table I). By multiplying the number of lesions by the severity index and adding the sums, a score indicating the total "acne load" was obtaining (1).

At every visit to the clinic the patients were photographed by a professional hospital photographer working exclusively with dermatological patients. The photographs were taken in a strictly standardized way. Kodacolor II daylight film was used throughout with, as light source, an electron flash (5 500°K) at right angles to the skin surface and an aperture setting of 11. On each occasion, three pictures were taken of the face, one from

Table I. *Definitions of types of acne lesions and their severity index*

A score representing the total "acne load" is obtained by multiplying the number of lesions of each type by the severity index

Severity index	Definition
1/2	Non-inflammatory comendones, open and closed (no erythema)
1	Comedones with surrounding erythema, superficial pustules in which the visible pus has a diameter of 2 mm at the most and with no, or little erythema
2	Pustules with a diameter exceeding 2 mm or pustules with a significant erythema
3	Deep infiltrates with or withour pustules: isolated cysts

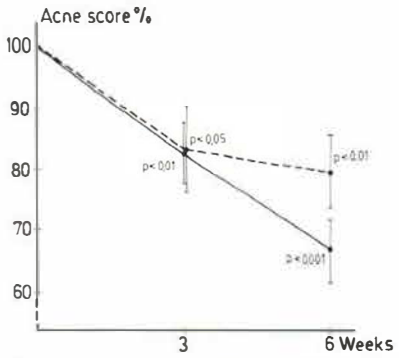

Fig. 1. Percentage change in acne score ± standard error of the mean (vertical range bars) and p-values after treatment for 3 and 6 weeks with placebo (– – –) or zinc (———).

the front and one from each side. The image of the patient's head occupied all the available space on the colour transparency.

At the visit after 6 weeks of treatment, the patients were asked to give their subjective opinion of the result, classed as either much improved, improved, somewhat improved, unchanged, worse, or much worse.

Two of the investigators (K. G. and S. L.) made an independent subjective evaluation of the overall results from the transparencies taken initially and after 6 weeks of treatment. The photographs were projected on a film screen, and assessment made in two stages. The first evaluation was made 4 months after the completion of the first part of the trial (37 patients). The second evaluation was made 4 months after the completion of the whole trial (54 patients). This time all the pictures were evaluated, even those which had already been evaluated one year previously. This was done in order to test the consistency of the assessment of the status of acne patients from film slides. All the evaluations of the photographs were done without either of the two clinicians knowing the type of treatment given to the patient in question. Nor did they know whether the pictures were taken before or after treatment. For the statistical calculations, pustules, infiltrates, and cysts were collected under one single heading. The statistical evaluations of the results have been made by using Student's t-test, Wilcoxon's rank sum test and χ^2-test.

RESULTS

Changes in the numbers of lesions and scores are shown in Table II and Fig. 1. Two patients in the placebo group could not be examined by the investigator making the initial lesion-countings at the 3-week visit and at the 6-week visit, respectively. Values from these occasions are thus missing. These patients have been excluded from the statistical analysis at the 3- and 6-week evaluation, respectively.

After both treatments a statistically significant

Table II. *Mean figures of lesions and acne scores before treatment and after 6 weeks of treatment in the zinc and placebo groups respectively*

	Zinc (n=27)			Placebo (n=26)		
Lesion types (severity index)	Before treatment	After 6 weeks of treatment (mean ± S.E.M.)	t-value	Before treatment	After 6 weeks of treatment (mean ± S.E.M.)	t-value
1/2	38.6	−13.8±2.5	5.48***	40.6	−16.3±5.7	2.86**
1	12.8	− 5.1±1.2	4.24***	12.0	− 2.8±1.0	2.81**
2–3	12.5	− 3.0±1.2	2.58*	11.5	+ 0.4±2.2	0.18
Total	63.9	−21.9±3.0	7.26***	64.2	−18.9±4.6	4.08***
Score	59.3	−18.8±3.4	5.56***	55.9	−10.8±3.8	2.80**
Score (%)	100	−33.4±4.8	6.97***	100	−18.3±6.0	3.06**

*=p<0.05. **=p<0.01. ***=p<0.001.

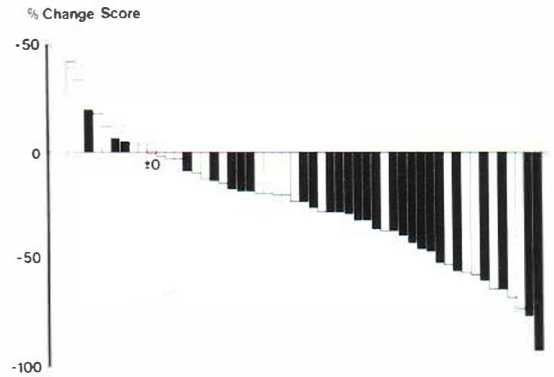

Fig. 2. The individual percentage change in acne score obtained by lesion counting after 6 weeks of treatment. □ Placebo; ■, zinc treatment.

reduction in the numbers of lesions and scores was evident. However, no statistically significant reduction between the third and sixth week was seen in the placebo group, whereas the reduction in the zinc treatment group was significant after both the first and the second 3-week period.

The results of treatment achieved in the two treatment groups were compared by a Wilcoxon's rank sum test (Table III). No difference was found after 3 weeks of treatment. After 6 weeks of treatment there was a significant difference in favour of the zinc group, regarding total numbers of lesions, scores, and the percentage changes in score.

The individual percentage changes in score are shown in Fig. 2. When comparing the number of patients in each group who showed a 50% improvement in score, no difference was found ($\chi^2=0.01$; N.S.). However, when comparing the number of patients in each group who showed a 25% improvement, there was a statistically significant difference between the two treatments ($\chi^2=6.83$; $p<0.01$). On analysing the patients' subjective opinion of the results of treatment after 6 weeks, no statistically significant difference was found ($\chi^2=2.31$; Table IV).

Evaluation of photographs

No difference in effect between the two types of treatment was found on evaluating the photographs. The overall results from the second evaluation, comprising all the 54 patients, are shown in Fig. 3.

The pictures of the first 37 patients were evaluated twice, with a year's interval. A comparison between the two evaluations showed great differences in results. One of us made equal assessments for 20 patients out of 37 and the other for 25 patients out of 37. Hence the probability of equal assessment is estimated as $p_1=20/37=0.54$ and $p_2=0.68$. Approximate 95% confidence intervals are (0.38; 0.70) and (0.53; 0.83), respectively.

Reported side effects

Two patients in the zinc treatment group reported slight indigestion during the first days of treatment, and 2 patients in the placebo group reported occasional nose bleeding during the trial period.

Table III. *Differences between treatments with oral zinc and placebo.*
The figures indicate the p-values obtained by Wilcoxon's rank sum test

	Acne grades			Total number	Score	% change score
	1/2	1	2–3			
3 weeks	0.84	0.16	0.53	0.65	0.69	0.99
6 weeks	0.33	0.10	0.08	0.03*	0.013*	0.007**

*$=p<0.05$. **$=p<0.01$.

Table IV. *The patient's subjective evaluation of the effect after 6 weeks of treatment*

	Much improved	Improved	Somewhat improved	Unchanged	Worse	Much worse
Zinc	3	7	9	7	1	–
Placebo	–	5	12	9	1	–

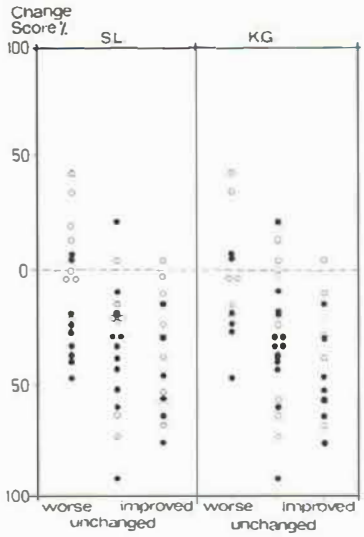

Fig. 3 The results of the evaluation of colour transparencies by two independent observers, compared with the acne score obtained by lesion counting after 6 weeks of treatment. ○, Placebo; ●, zinc treatment.

DISCUSSION

So far, three investigations into the effect of oral zinc therapy for acne vulgaris have been published. In the initial work by Michaëlsson et al. (2) a markedly beneficial effect of zinc vis-à-vis placebo was found as early as after 2-4 weeks, by using the lesion counting method. In another report from the same group, zinc was found to be as effective as oxytetracycline in acne treatment (3). On the other hand Weismann et al. (5) did not register any significant effect of zinc treatment at 4, 8, and 12 weeks.

In the present study, both zinc and placebo treatment gave a statistically significant decrease in the number of acne lesions and also in the acne score. After 6 weeks of treatment, the improvement in the zinc group was slightly better than in the placebo group. However, our results seem less dramatic than those reported by Michaëlsson et al. (2, 3). They found a decrease in acne score from 100% to about 35% as early as after 4 weeks of treatment (double-blind study) and after a further 8 weeks (open study) to 13% in their first work (2). In their second work (3) the corresponding figures were about 50% after 4 and 8 weeks and less than 40% after 12 weeks. These figures should be compared with our figures of a decrease in score to 67% after 6 weeks of treatment. Possible explanations for this discrepancy are certain differences in the design of the studies. The definitions of the various types of lesions are not identical. Nevertheless, it would appear that the results are influenced only to a minor degree by these differences. The present study was performed during the period of the year when no beneficial effect from exposure to the sun could be expected at the latitude in question. 45 out of the 54 patients completed the trial between November and January, when the average duration of daylight amounts to only 6 hours a day. The control of this parameter is indicated in (3) but not in (2). As has been pointed out by Weismann et al. (5) their study was performed in spring, to ensure that "all patients would achieve some alleviation of their acne". Thus it is possible that in their work the effect of the sun masked the weak beneficial effect of zinc on acne found in the present study. Our results show a mean reduction of the acne score by about one-third after 6 weeks. It is probable that the result is not optimal at this time. The study was designed at a time when preliminary investigations (Michaëlsson, unpublished) indicated a rapid effect of zinc treatment. Her later results and also our own clinical experience gained after the conclusion of this study make it probable that zinc therapy requires at least 3 months before full effect is obtained —as with most other forms of acne treatment (4). The follow-up period of 6 weeks may also be too short to compensate for variations due to menstruation, especially as the randomization allocated 8 females to the active group and 14 to the placebo group.

The marked placebo effect of acne treatment is well known. It is illustrated in Fig. 2. This figure must be regarded as a further, strong argument for doubleblind designs in clinical trials with acne treatment.

Studies on the same drug in acne treatment have often led to conflicting results. In a survey of the literature on tetracycline treatment of acne vulgaris, 6 trials revealed the tetracyclines to be significantly better than the placebo and 6 demonstrated no significant difference (6). From a clinician's point of view this is a somewhat surprising controversy. One explanation might be inadequacies in the methods used for measuring the effect of the treatment.

No objective methods are available for the assessment of the severity of acne vulgaris. They all rely on the subjective view of either the patient or, more commonly, the doctor. The doctor may try to

assess the actual state of acne by grading the results into various categories. He may also thake photographs for simultaneous comparison later on, or he may count each single lesion, give it a weighted value and hence calculate a total score that represents the severity of the disease.

In this study the acne status has been assessed by means of lesion counting, by the subjective opinion of the patient and by colour photography. Only by lesion counting was a statistically significant improvement found. This method thus seems to be a more sensitive way of assessing acne than either the patient's or the doctor's opinion. It also ought to be more reliable, as the investigator is forced to determine the type of each single lesion when the possibilities of doing so are optimal, i.e. when the patient is at the office. By continuous counting as in the present study, the investigator develops a personal standard for grading the lesions. Consequently the reliability of the procedure is best if only one person performs the counting. Two of our patients had to be withdrawn from the study because it was not possible to adhere to this principle, with great differences in the result as a consequence. In many works the doctor's overall judgement of changes in the acne status is the basis for the evaluation. It is probable that this judgement is greatly influenced by the opinion of the patient. It seems puzzling that a physician would be able to remember the details of an acne status from one visit to the other, weeks or months later.

Another relevant and important question is whether or not anything but the opinion of the patient should be taken into consideration. From a practical point of view this is of course the most important parameter. However, in investigative work such as the testing of new treatments, a more sensitive and precise tool certainly is needed.

It might be argued that photographs of good quality taken in a standardized way and assessed blind on one and the same occasion ought to be the most relevant procedure with regard to the clinical situation. Previous experience, both our own and others', have given us the impression that there are serious inherent difficulties with this method. This impression is substantiated by Fig. 3. As can be seen, there is a very poor correlation between the results according to lesion counting and the results obtained from the colour transparencies. Thus, patients with an improvement better than 50% according to lesion counting may be classified as unchanged when scrutinizing the photographs. One patient had a 92% reduction in acne score but was nevertheless classified as unchanged. This patient had mainly acne of the comedo type, i.e. erythematous lesions were very few. Even other non-erythematous lesions, such as deep infiltrates and cysts, could easily remain undetected on the photographs. On the other hand erythematous scars after previous acne lesions can be taken as active lesions.

Another result worthy of note is the lack of consistency between two assessments of the same photographs made by the same observers with an interval of one year. Despite the fact that the observers both were experienced dermatologists, only 20 and 25 patients, respectively, out of 37 were placed in the same category at the first and second assessment.

One pertinent question concerns the quality of the photographs. All reasonable precautions were taken to obtain good photographs, as stated previously. The only practical way of increasing the amount of information given by the photographs would be by taking close-up views.

In summarizing the results of the methodological part the following conclusions can be drawn. Lesion counting is the most sensitive method. It is also suitable for statistical analysis. The subjective impression of the patient and the overall evaluation by the doctor seem to be less sensitive and, at best, qualitative. Even good photographs are of limited value, their usefulness being restricted to more severe types of acne in which the erythematous components are predominant.

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S. Lidén, M.D.
Department of Dermatology
University Hospital
S-901 85 Umeå
Sweden