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Professional Paper

ZINC HYALURONATE IN THE TREATMENT OF DIABETIC FOOT ULCERS: A CONTROLLED RANDOMIZED OPEN-LABEL STUDY

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Key words: hyaluronic acid, zinc hyaluronate, diabetic foot, foot ulcers, neuropathic ulcer, neuroischemic ulcer

SUMMARY

The aim of the study was to evaluate the effect of zinc hyaluronate on neuropathic and neuroischemic diabetic foot ulcers in a controlled, randomized, open-label trial. Fifty-nine patients with 71 ulcers (44 neuropathic and 27 neuroischemic) were treated with standard methods. In 35 patients (43 ulcers), zinc hyaluronate (Hyaluricht, Gedeon Richter, Hungary) was added locally. The rest of 24 patients (28 ulcers) remained on conventional therapy. Ulcer healing was recorded in 93% of the Hyaluricht group and 82% of the control group, the mean time to healing being 74±31 and 92±25 days, respectively, yielding a significant difference between the two groups (p=0.008). For neuropathic ulcers, the rate of healing was 100% in the Hyaluricht group and 94% in the control group. Healing was achieved in 13/16 and 7/11 neuroischemic ulcers in the Hyaluricht and control group, respectively. These data show that Hyaluricht has a favorable effect on diabetic foot ulcers by promoting ulcer healing. The results obtained in this trial suggest that zinc hyaluronate could be included as an important element in the complex therapeutic approach for diabetic foot ulcers.

INTRODUCTION

Foot complications of diabetes mellitus present a major problem for clinicians as, at any time, 5% of the diabetic population will have a foot ulcer (1,2). This is a significant public health problem in itself, because the treatment and rehabilitation of patients with foot lesions are extremely demanding on the health care budget (3). The complicated diabetic foot appears to be a predominant indication for hospitalization of diabetic patients (3). Diabetic foot ulcers account for 50% of all non-traumatic amputations (4). Peripheral somatic and autonomic neuropathy together with peripheral vascular disease are the major risk factors for foot problems in diabetes (5,6), therefore the two main types of foot ulcers being neuropathic and neuroischemic ulcers. There are a number of signs differentiating vascular from neuropathic diabetic foot lesions (7). Simple, quick, inexpensive and reliable testing is available with regard to the severity of neuropathy, including vibration perception threshold, temperature discrimination, pressure and touch sensation with 10 g monofilament (8). Concerning peripheral vascular disease, the presence or absence of foot pulses on clinical examination is a good indicator of the existence of ischemia. A history of claudication is typical in the great majority of cases and can also be used for diagnosis (7).

The role of specific therapeutic interventions in diabetic foot ulcers, particularly local wound healing agents, is not yet understood. Hyaluricht contains two components, hyaluronic acid and zinc. Hyaluricht is the first drug containing zinc bound to hyaluronic acid; until recently, it has been considered that zinc ions cannot bind to hyaluronic acid (8). Hyaluronic acid is known to participate in many processes involved in wound healing, e.g., phagocytosis, epithelial and endothelial proliferation, angiogenesis, fibroblast activation, migration and proliferation (9-11). Zinc participates as a cofactor in more than 70 enzymes, some of which are involved in the biochemical processes of wound healing. Experimental data have suggested that there is an increased need of zinc in the granulation and re-epithelialization phases of healing (12). Thus, zinc hyaluronate has a complex effect on physiological wound healing, preventing the ulcers from infection because of its antimicrobial activity against a number of bacteria. It is a clear sterile solution with physiological osmolarity and pH 5-6. Hyaluricht does not affect the skin around the ulcer, and does not stick to the wound.

The aim of the present study was to evaluate the effect of zinc hyaluronate in the treatment of neuropathic and neuroischemic diabetic foot ulcers in a controlled, randomized, open-label trial.

PATIENTS AND METHODS

Fifty-nine diabetic patients with foot ulcers (37 male and 22 female), 27 of them with type 1 and 32 with type 2 diabetes, mean age 55.7±12.4 years and mean duration of diabetes 8.4±5.6 years, were included in the study. Fifty-one patients were treated with insulin, and eight were on oral hypoglycemic agents. Neuropathic ulcers were present in 32, and neuroischemic ulcers in 27 patients. As some patients had more than one ulcer, there were 71 ulcers in total, 44 of them neuropathic and 27 neuroischemic. The mean duration of ulcers was 6.7±4.2 months. All patients were treated with standard methods, i.e. debridement, local antiseptics (Jodasept), immobilization of the foot, and antibiotics if necessary. A group of 35 patients with 43 ulcers were treated with conventional methods and zinc hyaluronate. The rest of 24 patients with 28 ulcers remained on conventional therapy alone, and served as a control group. Zinc hyaluronate (Hyaluricht, Gedeon Richter, Hungary) was applied daily at a dose of 2-4 drops locally onto the ulcer. Eleven patients from the group additionally treated with zinc hyaluronate and ten patients from the control group were treated while hospitalized at the Department of Diabetology for a mean of 26±13 days, whereas others were treated as outpatients. Foot ulcers were classified according to Wagner scale (13) as follows: Wagner 1 - 35; Wagner 2 - 26; Wagner 3 - 8; and Wagner 4 - 2. The distribution of Wagner stages in the two groups was as follows:

Hyaluricht group W1 - 21, W2 - 16, W3 - 5, W4 - 1

Control group W1 - 14, W2 - 10, W3 - 3, W4 - 1

In the Hyaluricht group, there were 27 neuropathic and 16 neuroischemic ulcers. In the control group, there were 17 neuropathic and 11 neuroischemic ulcers. The following parameters were considered at entry and during the follow-up period until ulcer healing: ulcer depth (mm) and ulcer size (area in cm^2); duration of treatment and healing time; complications; final treatment result; and healing rate.

HbA_{1c} was measured at baseline and at the end of the follow-up period by DCA 2000.

Neurologic examination (reflexes, vibration perception threshold, temperature discrimination, pressure and touch sensation with 10 g monofilament), doppler sonography (AB index), and examination of peripheral foot pulses were performed to identify the type of diabetic foot ulcer.

Infection was present in 29 ulcers from the Hyaluricht group and 20 ulcers from the control group. The most commonly identified agent was *Escherichia coli* (n=21), followed by *Staphylococcus aureus* (n=10), *Proteus vulgaris* (n=19), *Pseudomonas aeruginosa* (n=8), some of them being found in combination in some ulcers. The distribution of different types of infection was quite similar in the two groups.

Statistical analysis was performed by the repeated measure analysis of variance (ANOVA), and results are presented as means ± SEM.

RESULTS AND DISCUSSION

Baseline ulcer characteristics in the two groups of patients are presented in Table 1. The patients were followed up until ulcer healing. The mean duration of treatment, i.e. time to healing, was 74±31 days in the Hyaluricht group and 92±25 days in the control group, the difference between the groups being significant (p=0.008). Hyaluricht was well tolerated by the

Table 1. **Baseline foot ulcer characteristics in Hyaluricht-treated and control groups of patients (mean ± SEM)**

Parameter	Hyaluricht group (n=43)	Control group (n=28)
Ulcer area (cm^2)	10.32±4.61	11.46±5.39
Ulcer depth (mm)	9.3±3.1	8.5±5.3

patients and no local or systemic side effect was reported. Infection was present in 67.5% of ulcers in the Hyaluricht group and 71.4% of those in the control group, which were accordingly treated with prolonged culture-guided parenteral and oral antibiotics (cephalosporins, lincomycin, Dalacin C, ciprofloxacin, amikacin). The lower rate of infection in the Hyaluricht treated group was probably due to the antimicrobial effect of zinc hyaluronate (10,11). The patient glycemia control slightly improved during the treatment period. So, the mean HbA_{1c} was 9.2±1.4% at baseline and 8.9±2.0% at the end of the follow-up; the difference between the two groups did not reach statistical significance. In the Hyaluricht treated group and control group, ulcer healing was recorded in 93% and 82% of ulcers, respectively. The evolution of foot ulcers is presented in Table 2. As seen from this table, 97.7% of neuropathic ulcers were healed (100% in the Hyaluricht group and 94% in the control group). Also,

Table 2. **Number of healed neuropathic and neuroischemic ulcers and ulcers of different Wagner stages in Hyaluricht-treated and control groups of patients (mean ± SEM)**

Ulcer type	Hyaluricht group (n=43)	Control group (n=28)
Neuropathic	27/27	16/17
Neuroischemic	13/16	7/11
Wagner 1	20/20	13/13
Wagner 2	16/16	9/10
Wagner 3	4/5	1/3
Wagner 4	0/2	0/2
Amputation	1	2

74% of neuroischemic ulcers (81% in the Hyaluricht group and 63.6% in the control group) were healed. Three of these were complicated and required minor amputation (one in the Hyaluricht group and two in the control group). The effect of zinc hyaluronate has not until now been investigated in diabetic foot ulcers despite its known complex effect on physiological wound healing (9-11). The results from this randomized, controlled, open-label trial demonstrate that zinc hyaluronate (Hyaluricht) has a favorable effect on diabetic foot ulcers by promoting ulcer healing. These data show that Hyaluricht could be included as an important element in the complex therapeutic approach to diabetic foot ulcers.

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