TOPICAL TREATMENT OF PRESSURE ULCERS

A Randomized Comparative Trial of Varidase® and Zinc Oxide

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Abstract. In a single-blind, randomized trial, the efficacy of topical streptokinase-streptodornase (Varidase®) solution was compared with that of zinc oxide on necrotic pressure ulcers in 28 patients. The effectiveness was determined by measuring the necrosis removal within 8 weeks. This occurred in 6 patients (43%) treated with Varidase® and in 7 (50%) treated with zinc oxide. The statistical tests applied showed no significant difference between the two treatments despite the use of a high power (1-β=0.95). The data suggest that the two regimens are about equally effective in the treatment of necrotic tissue.

Pressure ulcers are found mostly in elderly patients (Barbenel, Jordan, Nicol & Clark, 1977; Ek & Bo-man, 1982). Generally non-surgical measures are indicated in the management of these ulcers (Daniel, Hall & MacLeod, 1979; Morgan, 1975). The aim is to cleanse the ulcer of necrotic and dead tissue, prevent infection and promote healing (Reuler & Cooney, 1981). Many topical agents have been claimed to fulfil one or more of these requirements (Jacobsson, Rothman, Arturson, Ganrot, Haeger & Juhlin, 1976; Moberg, Hoffman, Grennert & Holst, 1983; Morgan). However, few have been adequately assessed under clinical conditions (Morgan).

Streptokinase-streptodornase (Varidase®) for topical application is an enzymatic preparation widely used in wound management (Hellgren, 1983). Streptokinase works indirectly by transforming plasminogen into the active proteolytic enzyme plasmin via streptokinase-proactivator complex. Streptodornase dissolves deoxyribonucleoproteins commonly present in pus (Hellgren). Varidase® is believed to be beneficial in the treatment of necrotic (Hellgren; Suomalainen, 1983) and infected wounds (Poulsen, Kristensen, Brygger & Delikaris, 1983).

Zinc administered systemically increases the rate of healing in zinc deficient patients (Hallboök & Lanner, 1972), although its mode of action is not fully understood. A double-blind, placebo-controlled trial showed that topical zinc oxide improved the healing of ulcers (Strömberg & Ågren, in press). The compound appeared to have a cleansing effect as well.

In an attempt to compare objectively Varidase® and zinc oxide in the local treatment of necrotic pressure ulcers, this randomized, open trial was carried out.

PATIENTS AND METHODS

Twenty-eight geriatric patients with one or more necrotic pressure ulcers were admitted to the trial. The ulcers studied ranged between 1 and 50 cm² in surface area and extended maximally to the subcutaneous fat. There were 20 women and 8 men in the study group, whose median age was 84 years (range 46–92 years). Twenty-four were hospitalized patients and 4 were out-patients. Nine patients had diabetes mellitus.

Patients were consecutively matched in pairs. Each member of the pair was randomly allocated to either topical treatment with Varidase or treatment with zinc oxide. The two groups were comparable with respect to age, sex and other characteristics shown in Table I. Patients assigned to zinc treatment were given dry, sterile gauze compresses premedicated with zinc oxide (400 µg ZnO/cm²). The Varidase solution (100 000 IU streptokinase and 25 000 IU streptodornase dissolved in 20 ml sterile isotonic saline solution; Lederle Laboratories) was applied on a sterile gauze compress. Zinc dressings were changed once a day and Varidase twice daily according to the manufacturer’s recommendations. Dressings were secured with porous acrylic-based tapes. In the case of multiple necrotic ulcers, these were treated uniformly, but only the largest was monitored. Before the study began, loosely attached necrotic material was removed, but ulcers were not surgically debrided subsequently. No pa-
Table I. Characteristics of the patients in the zinc and Varidase group

<table>
<thead>
<tr>
<th>Factor</th>
<th>Treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zinc ((n=14))</td>
<td>Varidase ((n=14))</td>
<td></td>
</tr>
<tr>
<td>Median age (yrs)</td>
<td>81</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Range (yrs)</td>
<td>46–92</td>
<td>75–92</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>9F</td>
<td>11F</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (no. of patients)</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Site of ulcer</td>
<td>No. of ulcers</td>
<td>No. of ulcers</td>
<td></td>
</tr>
<tr>
<td>Trochanter major</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ischial tuberosity</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower leg</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Malleolus</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Heel</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Lateral edge of foot</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sole</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base of big toe</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial ulcer area ((\text{cm}^2))</td>
<td>5.8</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Range ((\text{cm}^2))</td>
<td>1.2–26.0</td>
<td>1.2–18.2</td>
<td></td>
</tr>
</tbody>
</table>

Patients were given antibiotics. Nursing care followed the standard routine of the department.

The ulcers were photographed and the area was determined with a planimeter from \textit{in situ} tracings made by one of the authors (H.-E. S.) at weekly intervals. An independent surgeon from another hospital assessed the result of therapy from the photographs. It was judged 'successful' if the ulcer was free of necrotic tissue within 8 weeks—otherwise it was classified as 'unsuccessful'.

**Statistics**

The statistical test was performed at the 5% level, which means that the chance that concomitant variables (like age or initial ulcer area) or other random variables would cause a false significance is less than 5%.

We tested whether the probability of the patient being assessed as 'successful' was the same for the zinc and the Varidase group. For this statistical test the result was measured as 'successful' or 'unsuccessful'. The statistical test was designed to have the power of 0.95 to detect a 75% success rate in one group and a 25% success rate in the other. If a statistically non-significant difference was found it is reasonable to conclude that there is no large difference between the treatments. The number of patients needed with a conventional test (McNemar’s test) to achieve this power was too great to be practicable. Thus a sequential test procedure was used to minimize the expected sample size (Fig. 1).

The conclusions are valid for populations of the same kind as the one studied.

**RESULTS**

Disappearance of necrotic tissue occurred in 7 (50%) patients (4 women) treated with zinc and in 6 (43%) patients (5 women) treated with Varidase.

Table II. Effectiveness of treatment related to the initial area of the ulcers

<table>
<thead>
<tr>
<th>Treatment</th>
<th><strong>Free of necrosis</strong></th>
<th><strong>Not free of necrosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>((2.1–17.3))</td>
<td>((1.2–26.0))</td>
</tr>
<tr>
<td></td>
<td>(n=7)</td>
<td>(n=7)</td>
</tr>
<tr>
<td>Varidase</td>
<td>((1.2–11.7))</td>
<td>((1.2–18.2))</td>
</tr>
<tr>
<td></td>
<td>(n=6)</td>
<td>(n=8)</td>
</tr>
</tbody>
</table>
Comparison of Varidase and zinc oxide

Zinc

No. of untied preferences

10

5

0

5

10

15

Varidase

Fig. 1. Plan and result of the sequential analysis. When one zinc-treated member of a pair was assessed as ‘successful’ a mark was plotted in the diagram one step to the right and obliquely upwards. If a Varidase-treated member was assessed as ‘successful’ the mark was plotted one step to the right and obliquely downwards. If the plot crosses one of the solid borders a significant difference (at the 5% level) is established. If the plot crosses one of the broken lines (as in the present case), the null hypothesis cannot be rejected.

The sequential analysis revealed a non-significant difference between the two treatments (Fig. 1).

The treatment was discontinued and judged ‘unsuccessful’ in 3 patients in the Varidase group. In one of them Varidase caused a toxic skin reaction on the heel after 3 weeks of treatment. In another patient the necrosis on the lateral malleolus grew to eight times its original size. In the third patient a Pseudomonas aeruginosa infection developed in an ulcer on the heel after 6 weeks.

The initial ulcer area was larger in the zinc group than in the Varidase group (Table I). The ulcers which were cleansed were on the average half the size of the non-cleansed ulcers for both treatments (Table II). The median time to desloughing was 23 days (range 7–56 days) for the zinc and 21 (range 7–42 days) for the Varidase treated ulcers.

The zinc treated ulcers were reduced by 2.4% (median value) in surface area, whereas the Varidase-treated ones were enlarged by 18.7% (median value).

DISCUSSION

The removal of necroses is crucial in the local therapy of skin ulcers (Hagelbäck & Lundborg, 1982). The present investigation demonstrated that Varidase and zinc oxide cleansed pressure ulcers from necrotic tissue at about the same frequency within 8 weeks.

Larger ulcers were cleared of necrotic tissue to a lesser degree independent of the treatment (Table II). It therefore seems likely that the initial ulcer area plays an important role in the efficacy of treatment.

In addition to the cleansing effect, changes in ulcer size were measured. The zinc treated ulcers showed a tendency to decrease in surface area whereas those treated with Varidase tended to enlarge. This finding is in contrast to claims made earlier (Hillström & Pettersson, 1978). However, Hagelbäck & Lundborg noted that Varidase completely inhibited the growth of chicken embryo cells in a tissue culture assay using the dosage and duration recommended by the manufacturer. Varidase may therefore damage viable as well as non-viable cells in vivo. The tendency to increased ulcer area, observed in this study after Varidase treatment, may therefore be due to lack of healing and/or an excessive ulcer debridement.

One of the components of Varidase, streptokinase, is dependent on the presence of plasminogen for its action. Human plasma contains 0.2–0.3% plasminogen, while the concentration in wound exudates varies considerably; figures ranging from 0 to 62% have been reported (Åberg, Hedner, Jacobsson & Rothman, 1976). Streptokinase has optimal activity at pH 7.3–7.6 and the other component of Varidase, streptodornase, at pH 7.5 (Hellgren & Vincent, 1977). The therapeutic effect of Varidase could therefore vary with the individual condition of the ulcer.

Patients with pressure ulcers were found to have a lower serum-zinc level than the control patients (Abbott, Exton-Smith, Millard & Temperley, 1968). Several enzymes, e.g. proteases, require zinc for activity (Riordan & Vallee, 1976). Zinc also takes part in inflammatory reactions during wound healing (Tengrup, Ahonen, Rank & Zederfeldt, 1980). Topically applied zinc oxide is absorbed through
both intact and broken skin (Hallmans, 1978), thus, zinc oxide may affect many cellular processes involved in the cleaning of ulcers.

The fact that Varidase dressings must be changed twice a day and that they must be applied wet, whereas the dry zinc oxide dressings need to be changed only once daily makes a double-blind test impossible. Nevertheless, we conclude from our controlled study that Varidase and zinc oxide, in the form and dosage used here, are about equally effective in promoting the removal of necrotic tissue from ulcers.

REFERENCES