Effect of Low Frequency Pulsing Electromagnetic Fields on Skin Ulcers of Venous Origin in Humans: A Double-Blind Study

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Summary: The effect of an electromagnetic field on the healing of skin ulcers of venous origin in humans has been investigated in a double-blind study. Forty-four patients have been admitted to the study; one-half were exposed to active stimulators (experimental group) and the remaining to dummy stimulators (control group). The stimulation was scheduled to last a maximum of 90 days. The success rate was significantly higher in the experimental group both at day 90 ($p < 0.02$) and in the follow-up period ($p < 0.005$). The data suggest that the effect of the electromagnetic field lasts even when the stimulation is over. No ulcers worsened in the experimental group, while four worsened in the control group. Twenty-five percent of the patients in the experimental group and 50% in the control group experienced recurrence of the ulcer. It is concluded that stimulation with an electromagnetic field is a useful adjunctive therapy in the management of these patients. Key Words: Ulcer—Skin—Venous—Electromagnetic—Stimulation—Double-blind.

Low-frequency, low-energy pulsing electromagnetic fields (PEMF) have been used to promote the healing of ununited fractures since 1972. It has also been reported that when skin lesions were also present, their healing seemed to be enhanced by PEMF stimulation (4,5,13,18,28,30).

In the literature, opposite results in the healing of soft tissues in conjunction with stimulation with PEMF have been reported (7,9–12,14–16,20,24,25,31). It has been shown that exposure to PEMF in vitro favors collagen production by fibroblasts (23) and in vivo increases the tensile strength of healing skin wounds in the rat (17,21).

Chronic venous insufficiency (CVI) stems largely from several hemodynamic conditions that lead to a pressure increase within the veins of the lower limb. Chronic venous stasis may lead to skin ulceration (6). In our department, the standard treatment of these patients includes healing of the skin ulcer followed by treatment of the venous insufficiency, usually by saphena vein ligation or stripping (22).

We have investigated whether stimulation with PEMF could favor the healing of the chronic skin lesions of venous origin. These patients were chosen because these lesions are frequent, easy to be diagnosed, and have a clear etiology. The study was performed in a double-blind approach because it is well known that these ulcers can spontaneously improve or heal (6,7).

METHODS

Since 1985, 44 patients have been admitted to the study (28 females and 16 males, average age of 66 years). All had skin lesions present at least for 3
months. Patients treated with steroids or affected by systemic diseases were not admitted to the study. Patients with concomitant arterial occlusive disease were excluded. The presence of arterial disease was diagnosed with noninvasive instrumental investigations like Doppler continuous wave (c.w.), plethysmography, and oscillography.

Patients were randomly distributed to a control group (dummy stimulators) or to an experimental group (active stimulators) according to a computer-generated schedule prepared by a biostatistician: a random number seed was entered into the computer to generate a list that assigned equal number of active and control stimulators in blocks of four, two active and two dummy units. Nobody involved in the study was aware of the experimental conditions; the codes used to include patients in the control or active group were opened at the end, when all evaluations had been completed.

Ulcers were classified as idiopathic chronic venous insufficiency (I.C.V.I.) or postphlebitic venous insufficiency (P.P.V.I.), both leading to hemodynamic changes that are responsible for the ulcer. In the case of P.P.V.I., the hemodynamic changes stem from deep venous thrombosis. The ulcer classification was based on historical and clinical data, on Doppler c.w. vein analysis (ANGIODOP 482, D.M.S., 34970 Lattes, France), scanning the whole deep venous tree, or finally when necessary on phlebography (2,3,14,29).

No elastic compression was locally applied to the leg in patients of either group. Although compression is part of the routine treatment in our clinic, in this study it was omitted to be able to evaluate the effect of electromagnetic stimulation alone. Oral and local antibiotic therapy was always given concomitantly.

Patients were seen every second week. On each visit, a picture of the ulcer was obtained; together with a standard calibrating ruler, the blood glucose content and the erythrocyte sedimentation rate were measured, and the presence of bacteria in the ulcer was investigated. Every second visit, blood viscosity was measured by means of a Wells Brookfield LVT/D-CP cone plate viscometer (Brookfield Engineering Lab. Inc., Stoughton, MA, U.S.A.) (26). Every second visit we investigated erythrocyte filtrability (27), which indicates erythrocyte ability to change shape. Erythrocyte filtrability was measured by means of a REGATERM (Ghironi and Co., Buccinasco, Milan, Italy) using 5 μm filters (Nucleopore Corp., Pleasanton, CA, U.S.A.). At days 0 and 90, venous pressure was measured by Doppler ultrasound c.w. investigation (14).

On each visit, the patient was asked about the use of nonsteroidal anti-inflammatory drugs: 0 was given when the patient was using no drugs, 1 when he was using drugs less than once per day, and 2 when he was using them at least once per day. During the visit, an 11-cm-long analog scale was used to measure pain suffered by the patient.

To evaluate the patient’s performance, 0 was given when the patient could not work, 1 when his activity lasted less than 6 h, and 3 when the patient was not restricted in his activity.

The presence of malleolar edema was graded: 0 was given when no edema was present, 1 when minimal edema was present, 2 when it was evident, and 3 when the edema was quite large.

On each visit, the presence of granulation tissue was recorded, and the actual lesion was compared with the picture taken on the previous visit to evaluate if there had been some progression toward healing. The presence of granulation tissue at the bottom of the ulcer was considered to be an index of the presence of a repair activity; this step was followed by the epithelialization of the ulcer, which reduces the size of the ulcer. The ulcer was classified as healed when epithelialization was completed.

Patients were instructed to use the stimulator 3–4 h per day. The stimulation time was chosen on the basis of data reported in the literature (9,17,20). Patients were instructed to use the stimulator for a maximum period of 90 days, after which the stimulation was stopped. If the ulcer had not healed by this time, patients were maintained on a standard treatment including compression treatment, antibiotic therapy, oral daily use of bioflavonoid and derivatives, and local medication (22). The choice of at most 90 days of stimulation was made considering that this was expected to be the longest time required to activate the healing process, similarly to what we observed for nonunions (13,30).

The stimulation was carried out by the patients at home. To monitor patient compliance with our indications, a clock was placed inside each stimulator (dummy and active) to record how many hours the stimulator had been in use. The patients were not informed of the presence of the clock and they had no access to it.

Patients were instructed to position the coil on the ulcer. At day 90, the stimulator (Dermagen, Igea, Carpi, Italy) was sent back to the factory to
make sure it was functioning properly; at that time, the hours of use of the stimulator were recorded.

Active and dummy stimulators were absolutely indistinguishable from the outside both for their shape and for their weight. Active stimulators supplied the coil with a single pulse of electrical current generating a magnetic field of 2.8 mT at a frequency of 75 Hz, with an impulse width of 1.3 ms (Fig. 1). Dummy stimulators were manufactured so that the current flow in the coil was zero and no induced electric field could be recorded by means of a coil probe connected to an oscilloscope with a sensitivity of 100 μV/cm (8).

Assessment Criteria

At the end of the study, the pictures taken on each visit were shown to three different physicians unaware of the experimental conditions. Then they were asked about the efficacy of the treatment:

“excellent” implied that the progression of the ulcer had been very rapid and the treatment could be considered very effective; “good” that the ulcer had shown a good progression and the treatment had been effective; “inadequate” that the progression of the lesion had not been affected and the treatment had shown no efficacy compared to what expected; and “bad” that the ulcer had worsened.

The pictures taken on each visit were also used to calculate the area of the ulcer by means of an image analyzer (Tesak, TESAK, Florence, Italy) (8), using the area of the rule as a reference. By means of a camera connected to the computer, the picture was digitized and the area of the ulcer measured using the area of the ruler as a reference.

The statistical analysis of the data was made according to the criteria of the difference of the ratios.

RESULTS

Twenty-two patients have been included in the placebo and 22 in the experimental group. Three patients in the control group and four in the experimental one were excluded from our analysis. Three patients (two placebo and one active) stopped the use of the stimulator within 3 weeks; one patient per group used the stimulator discontinuously and on average less than 1 h per day; one patient (active group) suffered from an allergic reaction to drugs, and any treatment was stopped; and, finally, one patient admitted to the active group was diagnosed as having rheumatoid arthritis and was excluded from the study.

We thus studied 19 patients in the control group and 18 in the experimental group. Table 1 reports the characteristics of these patients.

None of the parameters investigated (erythrocyte sedimentation rate, glycemia, filtrability, erythrocyte viscosity, and venous pressure) had signifi-

TABLE 1. Characteristics of the patients studied

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>19</td>
</tr>
<tr>
<td>Males</td>
<td>6</td>
</tr>
<tr>
<td>Females</td>
<td>13</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>66</td>
</tr>
<tr>
<td>Range</td>
<td>25–82</td>
</tr>
<tr>
<td>Obese patients</td>
<td>9</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>2</td>
</tr>
<tr>
<td>Average age of the ulcer (months)</td>
<td>23</td>
</tr>
<tr>
<td>Range</td>
<td>3–240</td>
</tr>
<tr>
<td>I.C.V.I.</td>
<td>9</td>
</tr>
<tr>
<td>P.P.V.I.</td>
<td>10</td>
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cantly changed from the start of the stimulation to the end, and no difference was observed between the two groups at day 0 or 90 (Table 2). This strongly argues against any general effect of electrical stimulation.

At day 0, one patient had a small area of granulation tissue in the control group and none in the active group. At day 90 (among those patients not yet healed), 7 of 13 patients in the control group did present with granulation tissue, while the presence of granulation tissue was evident in all stimulated patients (6 of 6) of the experimental group ($p < 0.02$). The amount of pain was the same on both groups at day 0: 5.3 cm controls and 5.1 cm actives, average values recorded with the analogic scale. At day 90, pain significantly decreased in both groups: 1.7 cm controls and 0.7 cm actives. This difference is not significant.

At day 90, 6 patients (31.5%) were healed in the control group and 12 (66.6%) in the experimental one ($p < 0.02$).

The average healing was obtained in 76 days among dummy-stimulated patients and in 71 days among actively stimulated patients. On average, patients in the control group made use of the stimulator for 3.66 (3.1–4.5) h per day. Patients in the experimental group used the stimulator for 3.87 (3.2–4.9) h per day on average (Fig. 2).

According to the physican’s judgment during the visit at day 90, three patients in the control group and five in the stimulated group had still been improving since the previous visit. Two patients in the control group healed 1 and 9 months after the end of the inactive stimulation. In the experimental group, two patients healed 1 month and two patients 6 months after the end of the active stimulation.

Within 1 year from the start of the stimulation, 8 patients had healed among controls, an overall success rate of 42.1%, and 16 patients among patients using active stimulators, an overall success rate of 88.8% ($p < 0.005$).

All patients were followed for at least 1 year after healing. Over this period of time, in the control group, three ulcers recurred among those healed within 90 days and one among those healed after 90 days; in the experimental group, two ulcers recurred among those healed within 90 days and two among those healed after 90 days of stimulation. The overall healing at 1 year follow-up from healing was 4 patients in the control group (21%) and 12 in the active group (66.6%) ($p < 0.01$).

Researchers were asked to give an overall judgment in blind on the effectiveness of the treatment: 2 placebo and 5 active patients scored excellent; 8 placebo and 10 active patients good; 5 placebo and 3 active patients inadequate; and 4 placebo and no active patients scored bad. In 4 patients stimulated with a dummy unit, the ulcer worsened, while in no patient among active stimulated patients did we observe a worsening of the ulcer ($p < 0.05$) (Table 3).

The areas of all ulcers were measured. We found that among all ulcers healed within 90 days, the largest one was 14.9 cm$^2$ and was included in the control group. In an attempt to compare ulcers of homogenous size, we have distinguished two

![FIG. 2. Patient undergoing stimulation with PEMF. The coil is positioned on the bandages at the ulcer site.](image-url)
groups of ulcers: the ones larger than 15 cm² and the ones smaller than 15 cm², the latter being considered the largest size for an ulcer able to heal spontaneously within 90 days. Twelve ulcers in the control group had a size smaller than 15 cm² [average of 5.0 ± 3.3 cm², (SD)]; 14 ulcers were smaller than 15 cm² in the experimental group (average of 4.8 ± 2.9 cm²). At day 90, 6 of 12 (50%) healed in the control group and 12 of 14 (85%) in the experimental group ($p < 0.05$) (Fig. 3). Seven ulcers in the control group were larger than 15 cm² average area (39.9 ± 23.9 cm²) and four in the experimental group had an average area of 34.2 ± 15.5 cm². At day 90, the average area in the control group was 27.8 ± 18.4 cm² and 18.1 ± 18.8 cm² in the experimental group. The average size had decreased by 30% in the control group and by 47% in the experimental one. Within 9 months from the end of the stimulation, one of seven of these large ulcers healed in the control group and three of four in the experimental group (Fig. 4).

No significant difference was observed in the healing rate of ulcers according to their classification (I.C.V.I. or P.P.V.I.), the weight of the patient, or the presence of diabetes.

**DISCUSSION**

The possibility of spontaneous healing in the patients here is clearly demonstrated by the high success rate in the control group at 90 days (31%) and in the follow-up period (42%). The use of an active stimulator significantly increases the success rate of healing (66.6 and 88.8%, respectively).

The effect of 4 h of stimulation with PEMF, monitored with the clock inside the unit, is observed both in the case of small ulcers and in the case of large ones. According to the physician’s evaluation on the effectiveness of the treatment, 15 patients in the actively stimulated group scored good or excellent vs. 10 in the placebo group ($p < 0.05$).

All ulcers in the experimental group, whatever their size, showed the presence of granulation tissue beginning by day 15. This was still present at day 90 and led to healing of the ulcer in the late follow-up period. This indicates that the effect of the treatment was not completely lost with interruption of the stimulation.

These ulcers may spontaneously improve or worsen (7); in the control group, four worsened in-

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**TABLE 3. Assessment of the effectiveness of treatment**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Active</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>19</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>2</td>
<td>5</td>
<td>ns</td>
</tr>
<tr>
<td>Good</td>
<td>8</td>
<td>10</td>
<td>ns</td>
</tr>
<tr>
<td>Inadequate</td>
<td>5</td>
<td>3</td>
<td>ns</td>
</tr>
<tr>
<td>Bad</td>
<td>4</td>
<td>0</td>
<td>0.02</td>
</tr>
</tbody>
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*ns, not significant.*
pedicle skin flap survival and wound tensile strength (17). Again, these two effects can be explained by vascular invasion and collagen production. On the basis of this information in the literature, we can expect cellular activity, namely fibroblasts, and vascular invasion to increase in actively stimulated patients, leading to ulcer healing. These combined effects can explain the positive results obtained in actively stimulated patients vs. controls. We have found that granulation tissue was present in all actively stimulated patients since the first control visit (15 days after the start of stimulation) and it was still evident in all actively treated ulcers not yet healed at day 90. Conversely, granulation tissue was present only in 7 of 13 placebo-treated ulcers not yet healed at day 90.

The present research study, performed in a double-blind manner, using a homogeneous group of patients undergoing active or dummy stimulation, shows that 4 h of stimulation with PEMF significantly favors the healing of skin ulcers of venous origin. We conclude that stimulation with PEMF is useful in obtaining the healing of a very high percentage of ulcers, in a short time. However, healing is only the first step in the treatment of these patients; once it is obtained, the underlying hemody-
namic problem must be corrected, if possible, to prevent the otherwise certain recurrence (6,22) of the ulcer.

Acknowledgment: We thank Vincent R. Hentz for reviewing the manuscript. This paper was presented in Washington at the 8th Annual Meeting of the Bioelectrical Repair and Growth Society.

REFERENCES


