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Effect of Electromagnetic Fields on Patients Undergoing Massive Bone Graft Following Bone Tumor Resection

A Double Blind Study

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Massive bone allograft after tumor resection has been used for over 20 years. Many factors negatively influence the healing of the junction between the allograft and the host bone, resulting in a low healing rate and lengthy time to union. This study evaluated whether pulsing electromagnetic field stimulation could be advantageously used in these patients. A double blind prospective randomized study was designed. Eighty three host graft junctions in 47 patients were considered. The overall host graft junction healing rate was the same (67%) in both control and active stimulated patients. Although not statistically significant, a positive effect of pulsing electromagnetic fields was observed for those host graft junctions with a cortico-cortical contact between allograft and host bone. When adjuvant postoperative chemotherapy was not employed, a definite effect of pulsing electromagnetic field stimulation was observed: the healing time decreased from 9.4 months in the control group to 6.7 months in the active stimulated group ($p < 0.001$). This effect would have been lost if chemotherapy was employed. There was also no advantage in supplement with iliac crest autografts at the host graft junction site if chemotherapy was used. Factors that significantly influenced the host graft junction healing rate were: chemotherapy; type of allograft host bone contact; quality of host graft junction; and, in intercalary allografts, use of the osteosynthesis device. No difference was observed between control and active groups for patient survival or number of local or distal tumor recurrences.

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Low frequency low energy pulsing electromagnetic fields have been utilized to promote bone healing since 1974.[2,3,33] Their clinical use has been debated because there have been no reports of simultaneous or blind control groups.[14,30]

Recently, the positive effect of pulsing electromagnetic fields on bone healing has been demonstrated in double blind studies for nonunions,[32] delayed unions,[31] and osteotomies.[4,17] Moreover, understanding of pulsing electromagnetic field mechanism of action is significantly increased.[5,9,27,28] In vivo, in transcortical holes of metatarsal bone, pulsing electromagnetic fields have been able to increase both the mineral apposition rate, at early stages of osteogenesis, and the amount of newly formed bone at later stages.[6,7]

Pulsing electromagnetic fields have been studied for harmful or untoward side effects. In vitro, the exposure of human lymphocytes to pulsing electromagnetic fields of the type used in this study did not result in genotoxicity.[5] In vivo, the exposure to pulsing electromagnetic fields of both animals and patients with tumors did not cause tumor growth or negative side effects attributable to the presence of the electromagnetic field.[1,18,24,26]

The authors have been involved for many years in the treatment of patients with bone tumors and, during the last 10 years, have begun using allografts to replace the large bone segments removed. In these patients the biological and mechanical conditions are particularly complex when one considers the extent of the resection, the presence of the massive allograft, the chemotherapy often used in association with surgery, and the underlying pathology. All these factors make it difficult to achieve bone healing in these patients.[8]

This study investigated whether pulsing electromagnetic fields could increase the healing rate and shorten the time to union of host graft junctions in patients undergoing bone resection followed by massive allografts.

MATERIALS AND METHODS

To evaluate the effectiveness of electrical stimulation with pulsing electromagnetic fields in promoting allograft union, a double blind randomized prospective study of 50 patients was devised. For admission to the study, surgical results must have been adequate from an oncological point of view; patients with intralesional or contaminated resection were not included.

Patients were randomized to receive either active (experimental) or placebo (control) stimulators; the medical staff was unable to differentiate between them. The status of the stimulators was identified only after all patient evaluations were completed. To ensure uniformity between these 2 groups, the patients were divided into 8 categories based on factors known to influence allograft union.[10,11,13,23]

Thus, 8 categories were formed based on: age (<16 yrs or >16 yrs); whether adjuvant chemotherapy was administered, and whether autogenous grafts were used (Table 1). The patients were assigned either to the control or experimental group by order of admission to the hospital according to a computer generated schedule. A random number seed was entered into the computer to generate a list that assigned equal numbers of active and placebo stimulators (blocks of 4, 2 active and 2 placebo). Thus uniformity between the control and the experimental group was achieved.

Three patients were excluded from final evaluation because they interrupted the stimulation within 30 days. The male to female ratio was 23:24. The average age of the patients was 19 years (range, 8 to 43 years). Twenty three patients were in the control placebo group and 24 in the experimental active one. Thirty six patients (76.5%) had high grade malignancy tumors, 7 (14.9%) had low grade malignancy tumors, and 6 (12.7%) had benign tumors. Eighty three host graft junctions (osteotomies) in 47 patients undergoing allograft reconstruction following tumor excision were studied. There were 11 osteoarticular allografts, 12 diaphyseal intercalary allografts, and 24 allograft arthrodeses comprising 63 femoral host graft junctions, 16 tibial host graft junctions, 3 humeral ostetomies, and 1 radial host graft junction.

The host graft junctions were assessed radiologically at the beginning of the study to evaluate the type of contact between the graft and the host and the size of the gap at the osteotomy site. Of the 83 host graft junctions studied, 52 had predominantly cortico-cortical contact (both host and graft bone obtained from diaphyseal

TABLE 1. Patient Distribution

	Control (Placebo)	Experimental (PEMFs)
Group 1		
Age > 16 years		
Chemotherapy and Autograft	2	2
Group 2		
Age > 16 years		
Chemotherapy	5	4
Group 3		
Age > 16 years		
Autograft	0	1
Group 4		
Age > 16 years		
Control	8	8
Group 5		
Age <16 years		
Chemotherapy and Autograft	2	2
Group 6		
Age <16 years		
Chemotherapy	7	7
Group 7		
Age <16 years		
Autograft +	0	0
Group 8		
Age <16 years		
Control	1	1

cortical bone); 11 had mainly cortico-cancellous contact (host or graft bone obtained from metaphyseal spongy bone); and 20 had cancellous-cancellous contact (no diaphyseal cortical bone at the host graft junction) (Table 2). The osteotomies were excellent (no gap visible) in 51 host graft junctions, good (gap < 1 mm) in 16, and poor (gap > 1 mm or significant discrepancy between cross sections) in 16.

Autogenous iliac crest bone grafts were used in 12 host graft junctions (14%). Osteosynthesis was achieved by long plates in 37 host graft junctions and by intramedullary rods in 46 host graft junctions.

Every 2 months the patients were evaluated clinically and radiologically. The host graft junction was considered healed when bone extremities were united in both anteroposterior and mediolateral views.

If bone healing was not achieved 12 months

TABLE 2. Type of Allograft and Host Bone Contact and Postoperative Adjuvant Chemotherapy

Type of Contact	Cortico-Cortical		Cortico-Cancellous		Cancellous-Cancellous	
Pulsing electromagnetic fields	15	11	4	2	6	2
Placebo	18	8	3	2	8	4

* Postoperative adjuvant chemotherapy.
- No postoperative adjuvant chemotherapy.

postoperatively the host graft junction was considered a nonunion. The host graft junctions that had healed at 12 months after surgery were evaluated to determine whether any factors other than treatment with the pulsing electromagnetic fields may have affected allograft host union. The following parameters were evaluated: (1) the type of allograft (osteoarticular, intercalary, arthrodesis); (2) the effects of the anatomical location of the allograft; (3) the effects of the length of the allograft; (4) the quality of the host graft junction including the type of contact between the allograft and the host bone (cortico-cortical, cortico-cancellous or cancellous-cancellous) and the size of gap (when present); (5) the type of osteosynthesis (long plates or intramedullary nail); (6) the effects of chemotherapy; and (7) the effect of supplementing the host graft junction site with autogenous bone graft.

Patients signed an informed consent form. Within 7 days from surgery, patients were instructed to use pulsing electromagnetic fields for 8 hours every day for a maximum of 12 months. A clock was included in each stimulator to record the hours of use.

The electromagnetic field was generated by 2 inductively coupled coils (usually custom made). The coils were kept in place by a Velcro strap (Velcro USA, Manchester, OH). The pulse generator (IGEA, Carpi, Italy) supplied the coils with single voltage pulses at 75 Hz, each lasting 1.3 milliseconds.[4-7,17,33] The voltage of the pulse was set so that, at the host graft junction site, the electric field induced in a standard coil probe was 3.0 ± 0.5 mV (Fig 1). No electric field was recorded when dummy stimulators were tested. Fisher's exact test was used to compare the rates of union. The analysis of variance (ANOVA) was used when the effect of chemotherapy and pulsing electromagnetic field stimulation on times to union were compared.

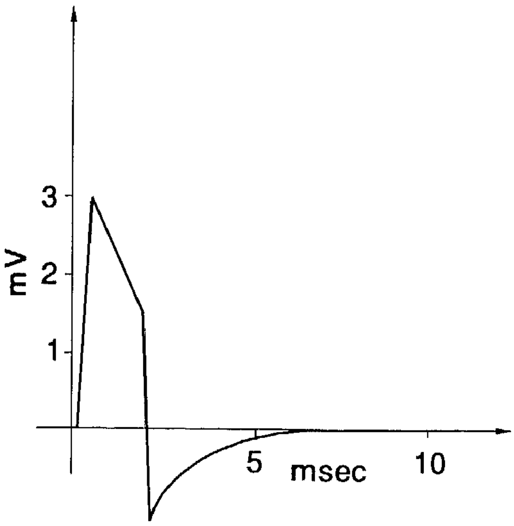

Fig 1. Waveform of the electric field induced in a standard coil probe.

RESULTS

Of the 83 host graft junctions (47 patients) that underwent allograft reconstruction following en bloc tumor resection, 56 (67%) had united within 12 months. Union at all host graft junction sites was achieved in 26 patients (55%). The number of patients and host graft junctions healed was the same in both the experimental and control groups. Union was usually by direct callus formation: periosteal callus formation was only seen in 7 of the host graft junctions that united. Followup was for an average of 28 months. After the 12 month period, 5 additional patients healed spontaneously, 9 healed following iliac crest autografts, 3 by plating and autografts, and 3 by vascularized fibula autograft. One patient did not heal.

There were no differences between the active and control groups in the number of patients alive with no evidence of disease, alive with local or metastatic recurrence of the disease, and deceased.

Stimulators were used for comparable periods of time in both the active and placebo groups, an average of 5.4 hours per day. Thirteen of 23 patients (56%) healed in the control group, and 13 of 24 (54%) in the active group. The overall rate of host graft junction union was 67%; 29 of 43 in the control group and 27 of 40 in the experimental group. The healing rate of intercalary host graft junctions was higher in the experimental group (62%) than in the control group (42%). Among patients who underwent an intercalary graft with 2 host graft junction lines of the cortico-cortical type, none healed in the placebo group, while 2 of 4 healed in the experimental group.

The average time to union for host graft junctions that received pulsing electromagnetic fields was 8.5 months. This compared favorably with an average time to union of 9.4 months for host graft junctions in the control group. The difference in time to union was highly significant only when host graft junctions that did not receive adjuvant chemotherapy were examined: 6.7 months to heal for patients who used pulsing electromagnetic fields (Fig 2) and 9.4 months for patients who used placebo stimulators.

In the control group the healing time did not differ if chemotherapy was or was not employed (9.3 versus 9.4 months); in the experimental group the healing time was 6.7 months if chemotherapy was not used and 10.4 months if it was. The analysis of variance with the factors, chemotherapy and pulsing electromagnetic field stimulation, was significant for their interaction: $F = 11.26$ and $p = 0.002$. The analysis of variance was conducted separately for the placebo and the experimental groups with and without the use of chemotherapy. The analysis was significant only for the experimental pulsing electromagnetic field stimulated group when chemotherapy was not used: $F = 17.72$ and $p = 0.0005$. These results indicate that the effects of chemotherapy counteract those of pulsing electromagnetic field stimulation.

No effect of pulsing electromagnetic field stimulation was found when the risk factors used for patient randomization were separately evaluated (Table 3). Also, pulsing electromagnetic field stimulation had no effect on host graft junction healing when the characteristics of the allograft (location, type, length, presence of gap) as well as the osteosynthesis device utilized were separately analyzed.

Allograft arthrodesis had the highest overall rate of union. Thirty eight of 48 host graft junctions associated with allograft arthrodesis united (79%), while only 54% of osteoarticular and 52% of intercalary allograft host graft junctions achieved union. Forty one of 63 host graft junctions carried out in the femur united (65%), while the rate of union for tibial host graft junctions was 81%. This difference was not statistically significant.

Union rate was independent of the allograft length, which varied from a minimum of 8 cm to a maximum of 22 cm. Fifty percent of the allografts used had a length between 14 and 16 cm.

The quality of the graft host junction had a direct relationship to the rate of union of the allograft to the host. Forty one of the 51 host graft junctions that were excellent (no gap visible) at the beginning of the study united (78%). The rate of union in host graft junctions with a gap > 1 mm was 5 of 16 that achieved union by the end of 1 year. This difference was statistically significant ($p < 0.02$).

The type of contact at the host graft junction site was also important. All 20 host graft junctions that had cancellous-cancellous contact at the beginning of the study united. Ten of the 11 (91%) host graft junctions that had primarily cortico-cancellous contact united, while only 26 of 52 host graft junctions (50%) that had cortico-cortical contact between the graft and the host united. Compared to the others, the healing rate of cortico-cortical host graft junctions was significantly lower ($p < 0.001$). This was particularly evident in patients treated with chemotherapy (36% healing rate).

Large dynamic compression plates or locked intramedullary nails were used to fix the allograft to the host bone. Intramedullary devices were never used in osteoarticular allografts. When an intramedullary nail was used to fix an intercalary allograft, in no case was union achieved. There was no difference in the rates of union between allograft arthrodeses fixed by long compres-

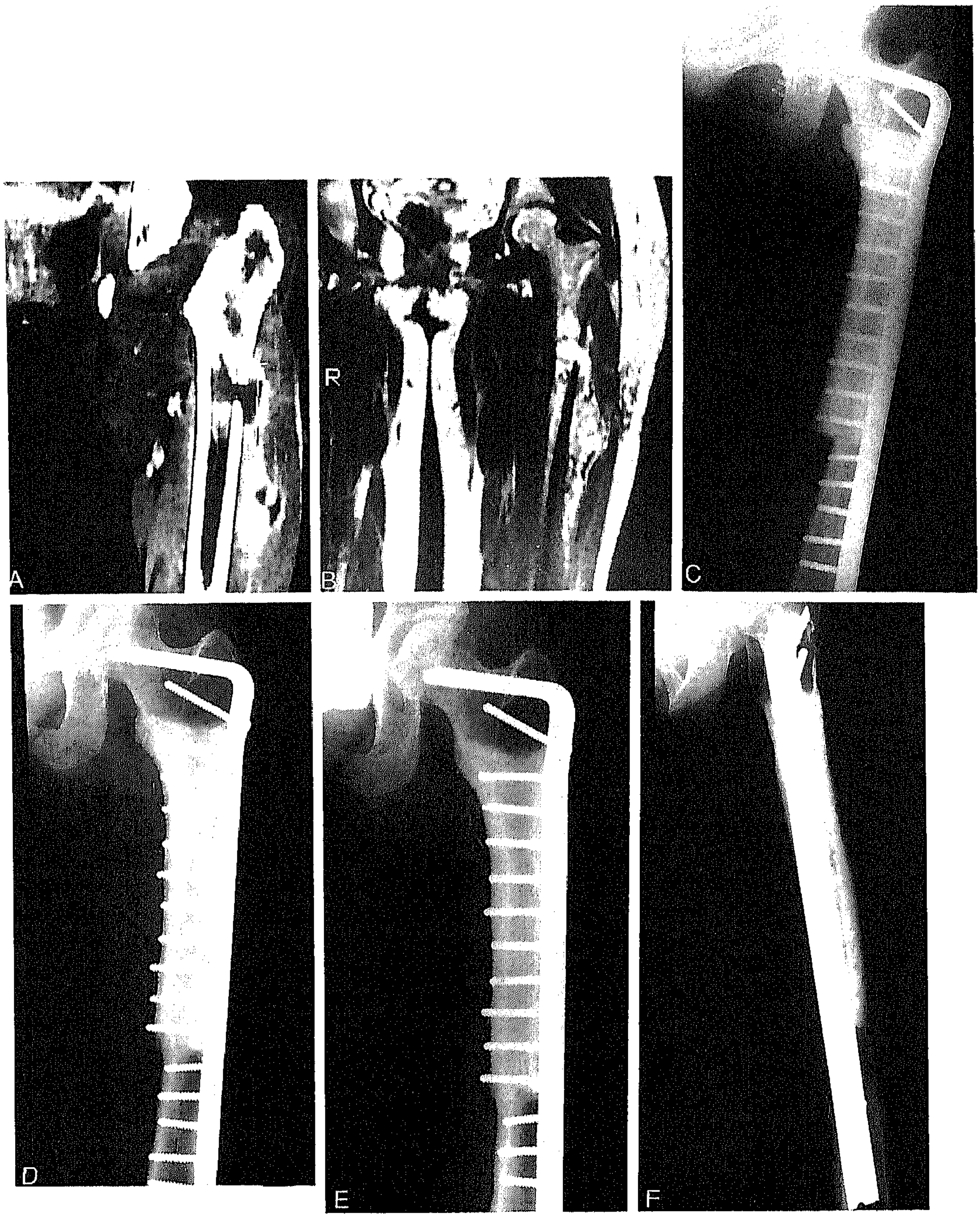

Fig 2A–F. Soft tissue sarcoma of the proximal thigh involving the femoral canal. (A) T2 weighted magnetic resonance image; (B) computed tomography scan reconstruction; anteroposterior radiograph of intercalary reconstruction of the proximal femur at (C) the start of pulsing electromagnetic field stimulation (cortico-cortical contact type), and (D) optimal fusion after 6 months of stimulation; (E) anteroposterior and (F) lateral views at 18 month followup.

TABLE 3. Effect of Pulsing Electromagnetic Field Stimulation and Risk Factors on Host Graft Junction

	Control (Placebo)		Experimental (PEMFs)	
Rick Factor	*Healed*	*Not Healed*	*Healed*	*Not Healed*
Age <16 years	18 (78%)	5 (22%)	15 (65%)	8 (35%)
Age >16 years	11 (55%)	9 (45%)	12 (70%)	5 (30%)
With chemotherapy	17 (59%)	12 (41%)	15 (60%)	10 (40%)
Without chemotherapy	12 (85%)	2 (15%)	12 (80%)	3 (20%)
With autograft	2 (67%)	1 (33%)	6 (67%)	3 (33%)
Without autograft	27 (67%)	13 (33%)	21 (68%)	10 (32%)

PEMFs = pulsing electromagnetic fields.

sion plates or those fixed by intramedullary devices.

There was a significant difference in the rate of union between patients who received adjuvant chemotherapy and those who did not; 32 (59%) of 54 host graft junctions united in the former group and 24 (83%) of 29 united when chemotherapy was not used.

In cortico-cortical contact host graft junctions, the healing rate decreased from 74% to 36% when chemotherapy was associated. For host graft junctions other than cortico-cortical contact no significant effect of chemotherapy was observed. When chemotherapy was used, 12 (36%) of 33 cortico-cortical host graft junctions united and 20 (95%) of 21 host graft junctions with noncortico-cortical contact united; $p < 0.02$.

Iliac crest autografts were used to augment 12 host graft junction sites, in 11 of these chemotherapy was used. Their healing rate was 63%, which does not differ from the 52% healing rate of host graft junctions not supplied with autogenous bone graft in which chemotherapy was used.

DISCUSSION

This double blind randomized prospective study was designed to evaluate the possible healing effect of pulsing electromagnetic fields. Data were collected on factors that are supposed to influence host graft junction healing. Their analysis thus allows a wider discussion on the problems connected with allograft healing.

One of the aims of this study was to see if pulsing electromagnetic field stimulation could increase the healing rate of the host graft junctions. Several problems have been associated with the use of allografts, such as nonunion of the graft recipient bone interface, resorption and fracture of the graft, and infection. Nonunion is a relatively common event[19–23,25,29,35] that is often a consequence of suboptimal bone contact at the junction site or inadequate immobilization.[15,35] It has also been proposed that nonunion may represent a subtle form of rejection.[15]

Of the 47 patients in this study 21 (45%) had a nonunion, whereas other authors reported lower figures (10–13%).[20] This difference can probably be explained by taking into consideration the characteristics of the patients studied here.

Sixty-two percent of the patients received postoperative adjuvant chemotherapy. Adjuvant chemotherapy or radiation therapy certainly favor nonunion.[16] Postoperative adjuvant chemotherapy is expected to have a negative effect on both the time to union and the rate of union.[10] Gebhardt et al[13] reported a 23% nonunion rate after allograft implantation when postoperative chemotherapy was used. In this study the nonunion rate increased from 17%–41% when chemotherapy was used. The effect of postoperative adjuvant chemotherapy was particularly evident when cortico-cortical host graft junctions were considered: the union rate dropped from 74% to 36% when chemotherapy was used.

Furthermore, nonunions are more frequent in segmental allograft reconstructions, which represent 86% of host graft junctions in the current study. Vincent et al[34] reported a 40% nonunion rate in intercalary resections of the lower limbs. In this study segmental allograft reconstruction nonunions were more frequent in intercalary resections (48%) than in arthrodeses (21%).

The incidence of nonunions was also affected by the osteosynthesis used. Better results were obtained when intercalary allografts were stabilized by means of rigid osteosynthesis than when intramedullary devices were used. None of the host graft junctions fixed with intramedullary devices achieved union.

Intramedullary fixation, even if locked, does not provide a satisfactory torsional stiffness and does not guarantee sufficient fixation and compression at the host graft junction sites. The allograft behaves as a passive framework devoid of any osteogenic activity, and instability or inadequate contact at the host graft junction sites inhibit the repair process.

The rates of host graft junction union among allograft arthrodeses were the same whether long compression plates or intramedullary devices were used.

The absence of an active periosteum of the muscles (resected for oncological reasons) slows down the healing process, which can take up to 1 year or more. This may help to explain the high rate of fatigue failures of osteosynthesis devices designed for fresh fractures (that heal in a considerably shorter period of time) when used in combination with allografts. The above considerations underline the need to randomize patients and to take into account several factors in the experimental design. Host graft junction healing is difficult in view of both the above biomechanical considerations and the low biological activity present at the host graft junction site.

Although the use of electrical stimulation did not increase the overall success rate in host graft junction healing, the authors' data indicate a positive trend when pulsing electromagnetic fields were used in intercalary allografts with both host graft junctions having a cortico-cortical contact. Pulsing electromagnetic field stimulation decreased the healing time of host graft junctions, and the effect became significant when adjuvant chemotherapy was not used.

This confirms what has previously been described for femoral[4] and tibial[17] osteotomies. When chemotherapy was not used pulsing electromagnetic field stimulation shortened host graft junction healing time by almost 3 months. This is important not only because of its relevance to morbidity, but also because an earlier fusion guarantees protection of both osteosynthesis devices and allografts from the risk of fatigue fracture.

The cytotoxicity of the postoperative adjuvant chemotherapy, which completely suppresses the effect of pulsing electromagnetic fields, indirectly confirms that electrical stimulation increases the cellular osteogenic response of bone at the host graft junction. The cytotoxic effect of chemotherapy may explain why supplementing the host graft junction with autogenous bone graft does not result in an increase in the healing rate.

This study demonstrates that pulsing electromagnetic field stimulation is safe and can be used to decrease the healing time of host graft junctions in cases for which postoperative chemotherapy is not required.

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