

Clinical Experiences with Low Intensity Direct Current Stimulation of Bone Growth

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The literature indicates that the local application of electrical energy is capable of stimulating bone growth.^{1, 12-15, 17, 18, 22-24} The questions now appropriate in regards to the clinical use of this modality are: safety, efficiency, optimum method of application and mechanism of action. In this paper we attempt to address these questions within the framework of our attempt to stimulate osteogenesis by the application of low intensity direct current to 13 patients over the past three years.

Our choice of direct current as the treatment modality is based upon our observations of the naturally occurring electrical events associated with fractures and other trauma,² which we have shown to be capable of producing the cellular changes associated with tissue healing in general.^{4, 16} Since at least the "endosteal" portion of the healing

fracture is considered to be a regenerative type healing process, our earlier observations on the similar electrical parameters associated with regenerative growth in general are supportive to this concept.^{3, 5-7} It should be noted that the naturally occurring electrical events associated with fractures show two distinct phases.⁵ Initially there is a relatively high voltage spike which decays over the first hour which we associate with the piezoelectric effect produced by the stress to failure and the subsequent short term period of material relaxation. This is followed by a long term direct current (DC) voltage which persists until the active cellular phase of the healing process comes to an end. This long term electrical phenomenon is similar to that noted during regenerative healing² and we consider it to be the result of the action of a specific analog type data transmission and control system.^{8, 9} In the case of fractures, we postulate it to be the stimulant for the "endosteal callus" formation. Our techniques are aimed at simulating this second phase of the electrical responses so as to "re-start" a cellular process identical to the original healing process. We postulate that this simulation of a naturally occurring mechanism may obviate any possible side effects that may be produced by the application of a non-biological type current. We have not yet attempted to duplicate the initial short duration impulse which we theoretically associate with the periosteal bone formation.

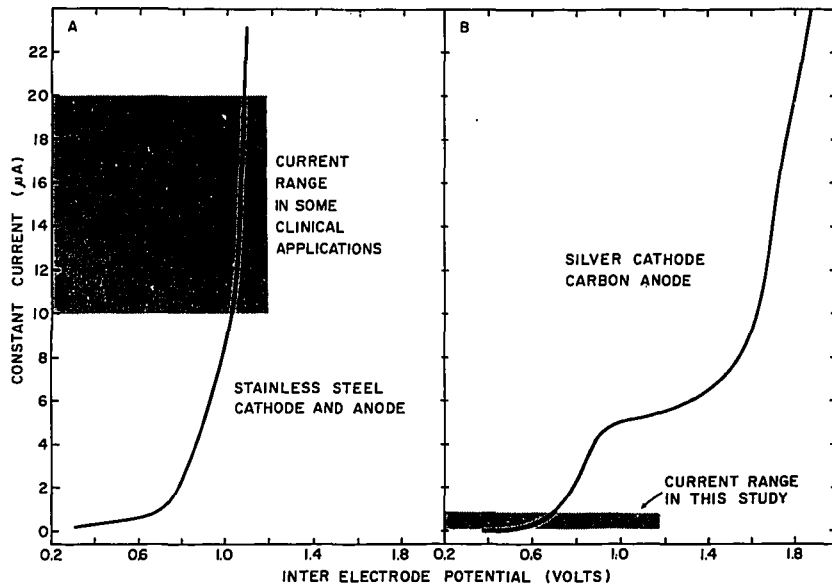
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FIGS. 1A AND B. Current vs. voltage curves for stainless steel cathode and anode combination, measured *in vivo*. Constant current was maintained for 15 minutes for each inter-electrode potential reading. The cathode (1.59 mm diameter, 1 cm exposed length) was implanted in the medullary cavity of a rabbit femur and the anode (stainless steel coil) was placed proximally on the abdomen with electrode paste. The curve demonstrates an expo-

ponential increase in current beginning in the range between 0.8 and 1.0 volts indicating a similar increase in the rate of electrolysis. The range of current administered in one reported clinical series utilizing this method of stimulation (12) is indicated by shading. (B) A similar curve also determined *in vivo* for a silver cathode (0.64 mm in diameter, 1 cm exposed length) implanted in the medullary cavity and a carbon-silicone rubber surface anode (techniques employed in our series). The behavior is considerably more complex with no true exponential increase in current noted until the potential exceeds 1.5 volts. The range of current employed in our series is indicated by shading and is well below any expected large-scale electrolytic region.

METHODS

The basic elements of our treatment consist of a single, pure silver, teflon insulated wire (0.64 mm in diameter) surgically inserted directly into the non-union site, which is made electrically negative (cathode) by an external direct current generator, and a carbon electrode applied to the skin surface as the positive pole (anode). The amount of current administered is determined by the length of non-insulated cathode implanted. This length is governed by local factors such as the specific site of the non-union and by the concept that the exposure of the local tissue to the current should be maximized. Initially, we began our series with currents of 100 nanoamperes (nA) per cm of cathode and we are presently operating in the region of 200 nA/cm.

In the non-unions complicated with osteomyelitis, we administered for the first 24 hours of treatment, current at the level of one microamperes (μA) per cm of electrode with the silver electrode driven positive. We have demonstrated that the silver ions emitted from such an electrode have strong bactericidal properties with a wide spectrum of activ-

ity.^{10, 20, 21} Although the volume so influenced approximates a cylinder of only one cm diameter around the electrode, it was postulated that this effect would be clinically useful in these cases.

The composition of the implanted electrode is particularly important in this circuit. It cannot be viewed as a passive conductor of the electrical energy, since its characteristics determine the voltage range in which electrolysis and other types of complex electrochemical reactions will occur in its vicinity. Only a few preliminary electrochemical investigations of electrodes for this purpose have been reported.^{11, 19} We chose 99.99% pure silver for the cathode because of its generally low interfacial resistance and stability of operation. We have avoided stainless steel and other alloys because of their complex composition, less stable operation and occurrence of electrolysis at lower currents and voltages. We have not yet tested other materials in pure form, such as platinum or gold and it is possible that silver is not the optimal material. An example of one type of testing procedure that should be followed in evaluating different electrodes *in vivo*

is illustrated in Figure 1. We are presently evaluating all other possible materials and combinations of materials in order to define the best material and the safe range of voltage and current within which it can be operated. It should be noted that during the time that the silver electrode is made positive, considerably less voltage is required to pass the same current as when it is the cathode.

The positive surface electrode is also important, since, when anodes, most metallic electrodes will emit metallic ions in all voltage and current ranges and display a different type of reaction in the region of electrolysis. In addition, since this is a surface electrode, its contact with the skin must be maintained at the lowest resistance possible to avoid increasing total voltage. We have utilized a carbon-filled silicone rubber disc of 6 cm diameter with Hewlett Packard Redux Creme and have encountered no local irritation or difficulty in maintaining good contact. This surface electrode is cleaned and re-applied and its position shifted alternately from proximal to distal to the fracture on a daily basis. There is a preferred current pathway between the implanted and the surface electrode and unless the position of the surface electrode is so changed, this could lead to stimulation on only one side of the non-union.

The basic elements of the external generator are illustrated in Figure 2. Physically the unit measures $4 \times 7 \times 10$ cm and is normally attached to the cast with adhesive tape. Not shown in the schematic are two sets of external jacks permitting monitoring of current and voltage without altering the generator output. Each unit mates with a charger unit and patients are provided with two generators and one charger. The generators are both set to the desired current level and the patients instructed to use one while charging the other, alternating on a daily basis. The charger units are provided with indicators permitting testing of the generator output as well as the level of battery charge.

RESULTS

In selection of patients for this type of experimental treatment we have attempted to be conservative. Patients either had attempts at standard treatment for non-union and subsequent failure or local factors, such as infection or deficient vascularity that mitigated against such standard treatment. We

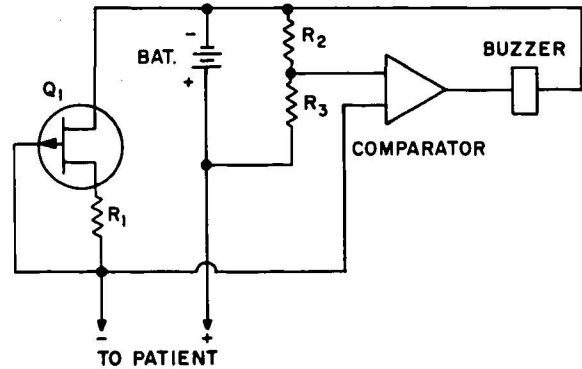


FIG. 2. Simplified schematic of low intensity direct current generator. Electric current supplied by the battery is controlled by the field effect transistor Q_1 and resistor R_1 . Current flow through R_1 establishes a feedback voltage applied to the gate terminal of Q_1 . This signal causes Q_1 to adjust its resistance so that constant current is applied through patient resistances from zero ohms to over one megohm. Changing the resistance of R_1 changes the magnitude of the current.

An alarm circuit, consisting of resistors R_2 and R_3 , the comparator and the buzzer, sounds an audible alarm when the voltage between patient leads exceeds one volt for any reason. This might indicate a dislodged surface electrode or dried out conductive creme. R_2 and R_3 form a voltage divider to establish a one volt reference voltage for the comparator. When the patient circuit voltage exceeds this reference, the comparator switches ON, sounding the buzzer. Interrupting the power from the battery or reducing the patient circuit voltage below one volt silences the alarm. Design is by Ritter Co., Rochester, N. Y. and is designated model "Vitron AG".

are reporting herewith every case and every instance of application of this experimental treatment since starting the study.

The clinical data on 17 separate attempts to stimulate bone growth by direct current is presented in Table 1. There were 13 patients involved, three of whom had more than one treatment. Included in the 17 attempts were: five non-unions of long bones that were non-infected, five infected long bone non-unions and 7 non-unions of joint fusions or synostosis, none of which were infected. In the five attempts on the non-infected long bone non-unions, there were two failures in

TABLE 1. Complete Data on All 17 Attempts at DC Stimulation of Osteogenesis

<i>Pt.</i>	<i>Pt. Age</i>	<i>Site Non-union</i>	<i>Age Non-union</i>	<i>Complications Non-union</i>	<i>Current Administered</i>	<i>Treatment Time (Days)</i>	<i>Total Energy (Joules)</i>	<i>Technical Complications</i>	<i>Result</i>	<i>Follow Up Time</i>	<i>Comments</i>
DC	48	Tibia	8 mo.	peripheral neuropathy	300–400 nA (–)	63	0.95	none	healed	31 mo.	Charcot type changes, diabetes, alcoholism, pre-treatment
WP	22	Femur	22 mo.	none	500 nA (–)	42	0.91	none	healed	27 mo.	
MT	46	Radius	22 yrs.	none	150–180 nA (–)	41	0.32	none	failed	36 mo.	
MT	46	Radius	22 yrs.	none	400 nA (–)	20	0.36	electrode breakage	failed	32 mo.	second attempt, same site
MN	28	Tibia double fx.	12 mo.	circulatory impairment	900 nA (–)	65	2.53	none	healed	4 mo.	proximal fx. treated distal fx. also healed. See Fig. 3
BF	47	Radius	3 yrs.	osteomyelitis	2 μ A (+) 300 nA (–)	1 20	0.26	electrode breakage	failed	34 mo.	
DK	46	Femur	2 yrs.	osteomyelitis	0.3 μ A (+) 300 nA (–)	1 43	0.56	none	failed	16 mo.	fibrous union, functional, no drainage
GW	56	Tibia	16 yrs.	osteomyelitis	3 μ A (+) 400 nA (–)	2 47	0.81	none	healed	30 mo.	one episode drainage since treatment
AB	25	Tibia	2 yrs.	osteomyelitis	6 μ A (+) 600 nA (–)	2 45	1.1	none	failed	16 mo.	fibrous union, functional, no drainage

TABLE 1. (continued)

<i>Pt.</i>	<i>Pt. Age</i>	<i>Site Non-union</i>	<i>Age Non-union</i>	<i>Complications Non-union</i>	<i>Current Administered</i>	<i>Treatment Time (Days)</i>	<i>Total Energy (Joules)</i>	<i>Technical Complications</i>	<i>Result</i>	<i>Follow Up Time</i>	<i>Comments</i>
NV	26	Tibia	6 yrs.	osteomyelitis	1 μ A (+) 900 nA (-)	2 56	2.18	none	healed	6 mo.	
CS	48	Tibio-talar fusion	1 yr.	none	300 nA (-)	62	0.8	none	healed	24 mo.	healed non-unions of talo-navicular & calcaneo-cuboid simultaneously
JR	49	Talo-navicular calcaneo-cuboid fusions	12 mo. 12 mo.	none none	200 nA (-) 400 nA (-)	33 33	0.28? 0.58?	electrical interference	healed failed	18 mo.	Two units used simultaneously; neither held electrical set point
JR	50	Calcaneo cuboid fusion	14 mo.	none	200 nA (-)	43	0.37	none	healed	14 mo.	second treatment for same site
HV	77	Knee fusion	5 yrs.	Charcot joint syphilis	465 nA (-)	28	0.56	none	failed	2½ yrs.	percutaneous electrode insertion
BF	49	radius-ulna-synostosis	10 mo.	none	210 nA (-)	67	0.61	none	healed	2 yrs.	synostosis attempted after previous attempt to heal non-union radius. Synostosis failed
TM	30	hip fusion	2 yrs.	none	300 nA (-)	48	0.62	none	healed	1½ yrs.	

the same case, an un-united Colles fracture of 22 years duration. In the first attempt on this patient, electrode breakage occurred sometime in the first four weeks of treatment. In the five cases of infected long bone non-unions, one failure was associated with electrode breakage early in the treatment course, one occurred in a grossly infected non-union of the tibia and a third occurred in a patient who had a non-union of a re-fracture through a site of prior osteomyelitis in the femur of six years duration. In none of the infected non-unions did the treatment cause an exacerbation of the pre-existing osteomyelitis and in all of these failures, the final result was a fibrous union that was functionally adequate and without drainage. In the 7 treatment attempts of joint fusion non-unions, there were two failures, one in a calcaneocuboid joint that was treated simultaneously with the talo-navicular joint of the same foot. In this case, two units were used simultaneously and electrical interference was noted between them. This same calcaneo-cuboid joint was later treated alone and healed completely. The other failure was in a failed fusion of a Charcot knee in a 77 year old patient with syphilis.

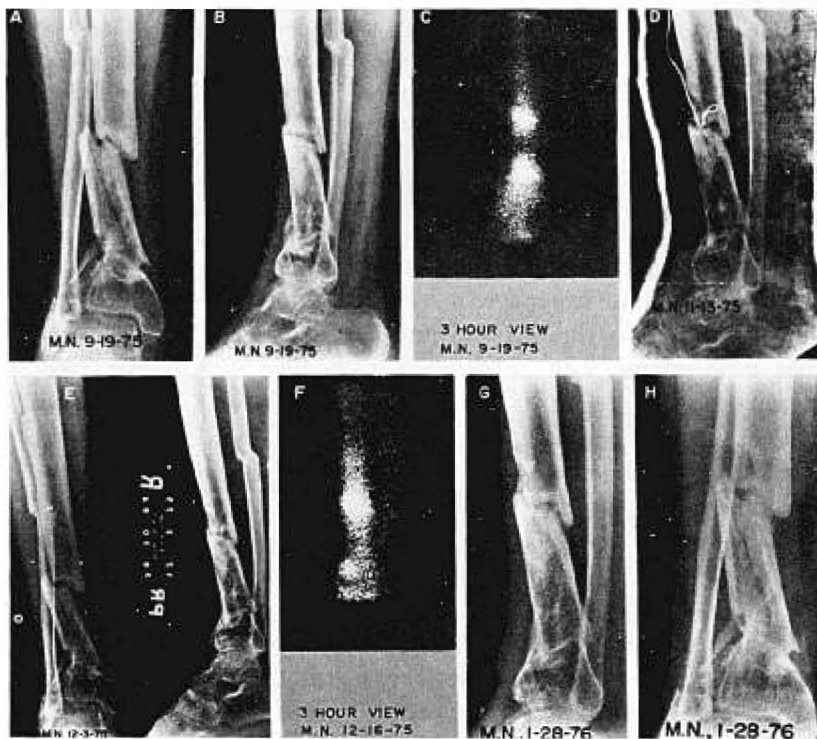
Overall, we have obtained a 10 out of 17 success rate based upon the total number of stimulation attempts. On the basis of the final result per patient, our success rate is 9 out of 13. The majority of our failures can be attributed to either technical problems, which we have subsequently solved, or to the nature of the case itself. Of particular interest are two cases in which a second non-union, remote to the site of the treated non-union, was healed simultaneously with the treated site. In the first instance, a patient with failures of attempted tibio-talar, talo-navicular and calcaneo-cuboid joint fusions was treated in the tibio-talar joint only, with subsequent fusions of all three sites. The second case was that of a patient with a double fracture of the tibia, treated at the proximal site only, who healed at both sites simultaneously. X-

rays and bone scans of this case are shown in Figure 3. Healing of the remote non-unions is attributed to the fact that some of the current passed through the remote site half of the time due to the daily movement of the surface electrode as previously described.

DISCUSSION

It is most interesting to compare the clinical results with the total energy administered. With two exceptions, patients receiving 0.61 Joules or more, healed regardless of their condition, while those receiving 0.56 Joules or less, failed to heal; again, regardless of the nature of their case. One exception was patient J.R., who initially was treated at two anatomically close sites with two units, using a common anode. The distribution of energy between the sites could not be determined because of the electrical interference noted between the units. One site healed and the second site was re-treated almost immediately. The energy delivered on this second occasion must be considered additive to that delivered during the previous treatment. We therefore feel that this patient must be excluded from the analysis of energy vs. bone stimulation. The second exception was patient A.B. who was treated with 1.1 Joules in a site of active osteomyelitis. Initially bone growth was noted radiographically and this increased in amount during the first 6 months. During this period of time the patient improved functionally as well. Over the past 10 months we have observed a resorption of the bone originally deposited and at this writing, the patient's status is essentially the same as when treatment was started. Despite the final failure in this case, the initial results were in keeping with the concept of total power vs. bone growth. Also of interest is the healing rate of the non-treated site in patient M.N. The treated site received 2.5 Joules and the untreated site received somewhat less than half of this energy as a result of the surface electrode position changes. The untreated site

FIG. 3. A 28 year old white male who incurred a compound fracture of the right tibia on 10/22/74; treated initially with debridement and reduction, immobilization and progressive ambulation. On admission 12 months after fracture, had established non-union of both fractures (A, B). Bone scans with Technician polyphosphate were done and flow studies indicated impaired circulation to proximal fracture and intermediate fragment. Three hour bone scans showed less isotope desposition in proximal fracture than in distal (C). On 9/30/75, treatment was



begun with a silver wire cathode inserted into the proximal fracture site (D). Surgical exposure was minimized to avoid further circulatory compromise. Treatment was terminated on 12/3/75. X-rays at that time were essentially unchanged (E); however, a bone scan on 12/16/75 now revealed a greater isotope deposition in the proximal fracture site than distal (F). This was taken to indicate active bone deposition in this area using the distal fracture as a control for both scans. On 1/28/76, the patient was bearing full weight in a short leg cast with no pain and clinically and radiographically, both fractures were healing, distal more advanced than proximal (G, H). The patient was seen at intervals in the clinic with continued progression. In May the cast was removed and ambulation with crutches began. In July, full weight bearing without support was started. When last seen in August of this year, the patient was fully ambulatory without complaint and had returned to college. At this time, clinically, both fractures were stable to mechanical stress and pain free. Radiographically, healing progressed in both fractures with, however, the proximal at a much slower rate. In August, the distal fracture was mature and remodeled, while in the proximal fracture, portions of the original fracture line were still visible.

healed at a noticeably faster rate than the treated site. This may be interpreted as indicating that the optimum energy input is in the 1 to 1.25 Joules range with the lower limit at approximately 0.6 Joules and the upper limit in the region of 2.5 Joules or slightly above.

In our earlier studies, we found that the use of a bifurcated silver electrode, with the limbs inserted into the medullary cavity proximally and distally, always resulted in electrode breakage. Since adoption of our

present technique, a single silver electrode, preferably traversing the non-union site, we have not had any electrode failures or encountered any difficulties in removing the electrode at the end of treatment. The present design of the low intensity direct current generator is stable and the alarm circuit enables the patient to monitor his own treatment as an out-patient. We have encountered no complications in the series thus far. The voltage and current levels employed appear sufficient to stimulate osteogenesis in a

majority of instances. Failures that have not been resolved by second attempts at treatment consist of cases of prolonged non-union, gross infection or neurological disease (Charcot joints). The technique of driving the implanted silver electrode positive for the first 24 hours of treatment in cases of non-active osteomyelitis appears to be safe and useful in avoiding exacerbation of this condition. At this time we have no evidence that it interferes with subsequent cathodic stimulation.

Our experience to date indicates that direct currents at physiological levels are capable of stimulating a significant osteogenic response in the human. The technique employed appears to be safe, obviating any possibility of local irritation or injury. The present clinical utility of this technique would appear to lie in the area of problem non-unions recalcitrant to standard methods of treatment. Present technical methods should be considered subject to revision as data are obtained on electrode behavior and further studies are performed at different current and voltage ranges. The results appear to be consistent with our concept of the electrical control system involved in normal fracture healing.

SUMMARY

Low intensity direct current stimulation of bone growth involves the continuous application of cathodic currents in the nanoampere range. The technique has been applied to 13 patients with a variety of non-unions and pseudarthroses with a success rate of 77 per cent. Preliminary data indicate that a range of total energy, from 0.6 to 2.5 Joules, is maximally effective. The technique has been combined with anodic control of local bacterial infection with promising results. Both the osteogenic stimulation and the bacterial suppression techniques as described in this paper, appear to be safe and effective.

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