THE EFFECT OF INDUCED ELECTRIC CURRENTS ON BONE AFTER EXPERIMENTAL OSTEOTOMY IN SHEEP

H. T. LAW, I. ANNAN, I. D. MCCARTHY, S. P. F. HUGHES, A. C. STEAD, M. A. CAMBURN, H. MONTGOMERY

From the Departments of Orthopaedic Surgery, Veterinary Surgery and Radiology, University of Edinburgh

We have investigated the effect of currents induced by electromagnetic fields on the healing of the tibia of sheep after osteotomy, using objective and quantifiable criteria wherever possible. A battery-powered, induction apparatus was developed and was enclosed within the cast applied to the limb, so that the treated fractures received pulsed magnetic fields for 24 hours a day while the animals were freely mobile. In all, 13 sheep were treated and 13 were used as controls.

The response was assessed by radiography of the limb and of the excised bone, by histology, including measurement of the areas of callus, fibrocallus and cortical bone, and by measurement of the uptake and extraction of bone-seeking mineral. All the bones healed and no statistically significant differences between the treated animals and the controls were discovered except (at only \( P < 0.05 \)) in the uptake of bone-seeking mineral; this increased more rapidly in treated animals over the two to three weeks after osteotomy, although at six weeks the uptake in both groups was the same.

Interest in the relationship between electrical fields and bone formation started with the work of Yasuda and his co-workers (Yasuda 1953; Yasuda, Noguchi and Sata 1954). They demonstrated the development of subperiosteal callus in bones subjected to continuous mechanical stress. In their initial experiments plastic pins passed transversely through the shaft of a rabbit’s femur were linked together by springs. The regions in which callus formed were shown to assume, under stress, a different electrical potential with reference to that of the periosteum. Yasuda speculated that this “callus without fracture” was formed as the result of the electric potentials induced by the applied mechanical stress, and he went on to show that similar callus formation could be stimulated by passing about 10 μA of continuous current along the bone.

In 1962 Bassett and Becker also demonstrated the electrical response of bone to stress and showed that the electric potential of those parts of the bone subject to compression became more negative, while those parts in tension became more positive. These effects, and the relationship between the stress, its duration and the electrical changes induced, have been investigated by Cochran, Pawlik and Bassett (1968) and by Dwyer and Matthews (1970).

The induced electrical activity is often ascribed to the piezo-electric nature of bone although, in terms of strict definition, living wet bone is not piezo-electric at all. There is now reasonable agreement that the electrical activity is due to streaming potentials (Eriksson 1974), resulting from the movement of ions in solution through transverse channels in the bone when these channels are distorted by mechanical stress.

The relationship between applied stresses and the architecture of bone has long been recognised (Wolff 1892) and it is tempting to speculate that electrical mechanisms are involved in the processes of bone remodelling. Numerous workers (Friedenberg et al. 1970; Marino and Becker 1977; Becker 1978) have reported that, when direct currents are applied, bone formation occurs mainly in the vicinity of the cathode. Increased osteoblastic activity would therefore be seen on the concave side of a long bone which is bending as a result of axial compression, that is, on the side under compression and consequently more negative in potential. This bone deposition would result in progressive realignment of the bone in a direction tending to equalise the compressive and tensile stresses, that is, towards an improved alignment of the bone to the direction of the applied force.

The question then arises whether electric currents will stimulate or accelerate repair following fracture, a question with obvious implications for the treatment of non-union. At least two types of therapeutic equipment

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H. T. Law, BSc, PhD, Senior Lecturer
I. H. Annan, FRCS Ed, Lecturer
I. D. McCarthy, BSc, PhD, Lecturer
S. P. F. Hughes, MS, FRCS, Professor of Orthopaedic Surgery
Department of Orthopaedic Surgery, University of Edinburgh, Medical School Buildings, Teviot Place, Edinburgh EH8 9AG, Scotland.
A. C. Stead, BVMS, FRCS, DVR, Lecturer
M. A. Camburn, BVSc, MRCVS, Lecturer
Department of Veterinary Surgery, Royal (Dick) School of Veterinary Studies, University of Edinburgh, Summerhall, Edinburgh EH9 1QH, Scotland
H. Montgomery, BSc, FRCS, Registrar
Department of Radiology, University of Edinburgh, Royal Infirmary, Edinburgh EH3 9YW, Scotland.

Requests for reprints should be sent to Dr H. T. Law.

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have come into widespread use. One provides a nearly constant current through wire electrodes which are inserted into the bone in the region of the fracture. The other uses a non-invasive method of producing a time-varying electric field in and around the fracture. One of a pair of coils is placed externally on each side of the fracture and fed with pulses of current to produce a pulsed magnetic field. The shape, duration, frequency and number of pulses in the pulse train are stated to be important in the production of the therapeutic response.

This paper describes the effects of the non-invasive, electromagnetic method on the healing of experimental osteotomies in the sheep tibia. The assessment of response included measurements of mineral extraction from the blood perfusing the bone (Hughes et al. 1977) and a weekly measurement of the uptake of bone-seeking radionuclides at the site of the osteotomy. These measurements were chosen as being objective and readily quantifiable. Histological and radiographic assessments also were made.

METHODS

The electromagnetic stimulator. Details of the pulse shape produced by the Bio-Osteogen equipment are not published, and we do not know how much the parameters of the pulse may vary from one set of equipment to another. In a comparable trial of treated and control osteotomies, it seemed essential that the form of current pulse to the coils should be accurately known and, within experimental limits, should be the same for each set of equipment. The parameters which were measured and controlled were the peak current (i_max), the time of rise and fall of the current (di/dt), the pulse length (t_p), and the frequency of pulse repetition. It also seemed essential that the current waveform be independent of variations of supply voltage within the range seen in battery-driven apparatus.

A driver amplifier circuit was designed to meet these objectives. The voltage waveform driving the amplifiers derives from a capacitor charged from a constant-current source. This gives a near linear rising voltage of about 1.5 × 10^4 V·s^{-1}. This is fed to two integrated operational amplifiers which each drive one coil through a common-emitter output stage. The emitter resistors are each of 15 ohms so that the rate of rise of current in the coils is about 1000 A·s^{-1}. The falling portion of the current waveform is similarly controlled by discharging the capacitor at constant current. Solid-state switches determine the charge and discharge times, and the duration and frequency of repetition of the pulse.

These arrangements ensured that the parameters of the waveform were not significantly affected by changing supply voltages, important in animal work since it was considered essential that the equipment be battery-powered so that it could be carried by the animals. The use of batteries imposes limitations of supply voltage, and in this instance the maximum available was less than 24 V. If an adequate rate of change of magnetic field is to be achieved, this sets a limit to the coil inductance which can be used. Coil inductance could be reduced by decreasing the number of turns but this would require a proportionate increase in the current, which is limited by the capacity of the battery.

A satisfactory compromise was achieved by using a pair of coils, each of 790 turns of 0.2 mm diameter enamelled copper wire, with a rectangular winding cross-section of 15 × 7 mm and a mean coil diameter of 52.5 mm. These were energised from two sealed rechargeable 12 V batteries of 1.8 Ah capacity, each weighing about 0.85 kg. This apparatus would operate comfortably for more than 24 hours, so that a daily charge and recharge routine could give virtually continuous treatment. The coils were incorporated in the outer layers of the plaster cast which had been applied to the osteotomised limb. The electronic driving circuit was encapsulated in silicone rubber and also contained in the cast. The batteries were in a canvas saddle-cloth on the animal's back.

The rate of change of magnetic field which was chosen was based on measurements made on a particular Bio-Osteogen apparatus. A search coil of 7 mm diameter, with 41 turns on the axis midway between the two coils spaced 8 cm apart, produced a peak output voltage of 14.5 mV, indicating a maximum rate of change of magnetic flux of 9.2 tesla per second (T·s^{-1}) at the point of measurement.

Our apparatus produced the near-trapezoidal current waveform shown in Figure 1. At the midpoint of a pair of coils 7 cm apart the peak field is 1.1 × 10^{-3} tesla and the rates of change of field are approximately 6.5 T·s^{-1} with the field increasing and 11.1 T·s^{-1} with the field decreasing. Full details of the parameters of field and pulse are given in Table I.

Experimental osteotomy. Adult blackface sheep of about 45 kg body weight were used. Under halothane anaesthe-
sia the right tibia was exposed from the medial side and a transverse osteotomy was made with a Stryker oscillating saw at the junction of the middle and distal thirds of the bone. The bone ends were then held in anatomical position by a nylon plate and six nylon screws with standard metric threads and countersunk heads. The bone was prepared with standard metric drills and taps. In the first few experiments 5 mm screws were used but two plates separated from the bone because screws fractured just below their heads. The screw diameter was then increased to 6 mm and there were no further failures or, despite the unusually fine pitch of the thread, any instances of screws pulling out of the bone.

After wound closure, the limb was placed in a plaster cast with an overlay of Baycast resin-impregnated bandage. The two coils, fitted only in sheep to be treated, were placed on opposite sides at the level of the osteotomy and held with more plaster and Baycast bandages. The control animals had an osteotomy and were plated and had casts applied in the same way, but they did not carry coils, pulse circuit or batteries. Weight-bearing was allowed immediately after operation. Of the 26 animals used, 18 were followed for six weeks, and a later group of eight sheep for two weeks only.

**Measurement of extraction.** The nutrient artery of the right tibia was exposed by a lateral approach (Davies, Bassingthwaighte and Kelly 1976). The artery was entered with a 0.64 mm diameter cannula and perfused at 2 ml per minute with heparinised autogenous whole blood using a Harvard pump. The venous outflow was collected from the ipsilateral femoral vein, using a 5 mm diameter cannula. Venous blood was collected in 5-second aliquots for 2.5 minutes after the injection of a bolus of tracer into the nutrient artery.

This bolus contained two labelled tracers, 3.7 MBq of $^{99m}$Tc-labelled methylene diphosphonate (MDP), a bone-seeking mineral, and 0.37 MBq of the reference tracer $^{125}$I-labelled albumin. A 1 ml sample from each aliquot of venous blood was assayed in a scintillation detector and counter to determine the content of each tracer.

The fraction of the injected tracer appearing in the venous outflow per second, at time $t$ after bolus injection, is defined as

$$h(t) = \frac{F}{I} C(t)$$

where $F$ is the flow in the cannulated femoral vein, $I$ is the total injected dose of radio-labelled tracer and $C(t)$ is the concentration of the tracer in the outflowing blood at time $t$.

The extraction ($E$) is defined by

$$E(t) = \frac{h_R(t) - h(t)}{h_R(t)}$$

where $h_R(t)$ denotes the fraction of the reference injectate (albumin), and $h(t)$ the fraction of the test tracer (methylene diphosphonate), appearing per second in the venous outflow at time $t$. Curves of $E(t)$ versus time may be plotted (see, for example, Figure 3) from the values of $h(t)$ and $h_R(t)$ given by the outflow dilution curves. The maximum instantaneous extraction, $E_{\text{max}}$, is taken to be the best measure of extraction before back diffusion occurs (Bassingthwaighte 1974).

$E_{\text{net}}$ is the cumulative extraction by the bone at a given time, $t$, and may be calculated from the equation

$$E_{\text{net}} = \frac{\int_0^t [h_R(t) - h(t)] \, dt}{\int_0^t h_R(t) \, dt}$$

**Radionuclide uptake.** The uptake of labelled bone-seeking mineral in the region of the osteotomy was measured at weekly intervals. $^{99m}$Tc-MDP was injected systemically and the count rate was measured 1, 5, 15 and 60 minutes after injection, using a portable scintillation counter over the osteotomy site. The same counter was used to determine the total activity of the injection before administration and the residual activity in the syringe after injection in order to determine the exact quantity of labelled diphosphonate which had been given.

**Histological assessment.** The sheep were killed after the extraction measurement and each tibia examined histologically. Standard 3 cm blocks of bone from the osteotomy site were decalcified, sectioned longitudinally and stained with haematoxylin and eosin. Scale drawings were made from projected sections and their different tissue components identified. These drawings were examined on a Reichert-Jung videoplan image analyser to measure the areas of cortical bone, woven bone callus and fibrocallus in a standard area from each section. Ratios of the areas of these three tissue components to each other were calculated.

**Radiographic assessment.** The image analyser was used also to measure the total areas of mineralised callus on the lateral and anteroposterior radiographs of the dissected tibiae of the six-week group. Correction for magnification was made by reference to the known distance between two of the plate holes.

In addition, a separate radiological assessment was made of the healing fractures on the latest available films.
of the living limbs. These films were evaluated "blind" by a panel of four assessors acting independently. Points were given for stage of healing on a scale from one to four for the following: early callus formation; good callus formation; early healing, with callus margins well seen; and early trabeculation, or healed fracture.

RESULTS
All the animals recovered uneventfully and took weight on their limbs soon after recovery from anaesthesia. All the wounds healed by first intention without infection, and at six weeks all the fractures were clinically united, with minimal displacement; angulation was under 5° in 42% and under 10° in 82% (except for the animals in which screws had failed). Abundant external callus was obvious. None of the animals killed at two weeks had bony union, but all the fractures were stable to rotation and displacement and the whole bone could be readily dissected free of muscle.

Extraction of ⁹⁹ᵐTc-MDP. Typical outflow dilution curves are shown in Figure 2, and the derived instantaneous extraction curves are given in Figure 3. The maximum instantaneous extraction (Eₘₐₓ) in this case was 0.49. Values of Eₘₐₓ, Eₙₑₜ, and the total fraction of the reference tracer recovered are given in Table II.

At the start of the experiments the extraction measurements were made six weeks after osteotomy. It was difficult at first to find a satisfactory method of cannulating the vessels and of collecting the aliquots. In the first four animals too low a fraction of the reference tracer was recovered for a reliable calculation of extraction, so these results were discarded. The six-week group in Table II shows results, therefore, for 14 animals (7 treated and 7 control). Eight animals (4 treated and 4 control), later in the series, were measured two weeks after osteotomy, for reasons which will become evident from the early results of the uptake measurements.

The mean values for maximum instantaneous extraction (Eₘₐₓ) and net extraction (Eₙₑₜ) show no significant differences between the treated and the control animals. The results from the six-week group were very similar to those from the two-week group; in both, the differences in mean values are small compared with the standard deviation.

Table II. The values of Eₘₐₓ and Eₙₑₜ for mineral extraction (see text). The results from 22 sheep (11 treated, 11 control) were derived from outflow dilution curves measured either six weeks or two weeks after osteotomy.

<table>
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<tr>
<th>Animal number</th>
<th>Eₘₐₓ</th>
<th>Eₙₑₜ</th>
<th>Recovery %</th>
<th>Animal number</th>
<th>Eₘₐₓ</th>
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Fig. 2
Outflow dilution curves for bone-seeking and reference tracers.

Fig. 3
Instantaneous (Eₘₐₓ) and net extraction (Eₙₑₜ) values derived from the outflow dilution measurements.
and the nine treated animals making up the six-week group. It can be seen that, although the short-term uptake of treated and control animals is very similar five weeks after osteotomy (the latest time at which these measurements were made), there appears to be a more rapid progress towards the final value in the animals treated with magnetic fields. Student's unpaired t-test shows these results to be significant only at the level $P<0.05$ for measurements made two weeks after osteotomy, and 60 minutes after injection of the bone-seeking mineral, and at $P<0.1$ three weeks after osteotomy, at 15 and 60 minutes after injection.

As had been expected, there was considerable variation in the activities measured in different animals. The variations from animal to animal were generally similar at each weekly measurement; those recording a high activity after one week tended to do so at the second and subsequent weeks. Figures 6 and 7 show the mean values of the increase in activity for each animal tested each week. The differences between the groups now emerge more clearly, the significance level for the weekly differences from one to three weeks after osteotomy being $P<0.05$ for the 15 and 60-minute measurements.

**Histology.** On histological examination there were no qualitative differences between control and stimulated bones from sheep killed at two and at six weeks. The measured areas of cortical bone, mineralised callus and fibrocallus in the sections showed no significant quantitative differences between control and stimulated groups either at two or at six weeks, either absolutely or in ratios between the three types of tissue.

**Radiology.** Mineralised callus was detectable in small quantities on radiographs from two weeks after osteotomy in both control and treated groups. The volume of callus increased and by six weeks a large amount of bridging callus was present. No differences could be detected between control and treated animals in any of the weekly films. Assessment of the six-week radiographs...
was done by four observers acting independently. The mean value and standard deviation for eight cases in the treated group was 11.50 ± 4.90 and for nine in the control group was 10.78 ± 2.90. The best possible result would have scored 16 points and again there was no significant difference between the two groups.

DISCUSSION
We tried to determine whether electromagnetically induced electric currents have an effect on the healing of osteotomised bone, using criteria which we felt to be, wherever possible, quantifiable and objective. The measurement of mineral extraction was used in sheep for the first time, extending previous work on dogs (Davies, Bassingthwaighte and Kelly 1976; Hughes et al. 1977; Hughes et al. 1978; McCarthy, Hughes and Orr 1980; Lemon et al. 1980). Satisfactory methods of cannulating the nutrient artery of the tibia and the femoral vein were developed, and it was shown that recovery of the labelled reference injectate from the femoral vein was high (Table II).

The sheep tolerated the procedure without obvious distress, and all were active soon after recovery, all the osteotomies healed within six weeks, and there were no soft-tissue complications or infections. The sheep appears to be a very suitable experimental animal for this work, being docile, relatively cheap to obtain and maintain, and, age for age, providing uniformity of size and physical condition.

The electromagnetic treatment unit which was developed can be used in experiments on large animals, the problems of designing a portable battery-powered device having been overcome. The pulse waveform provided is not identical to that of the commercial equipment, but the rate of change of magnetic flux, which we consider an important parameter, does correspond.

The use of non-conductive devices for internal fixation is considered to be important in experimental studies of the role of electricity in the healing of bone. The therapeutic response is not known to be inhibited by the presence of electrically conductive structures, but there is no question that considerable local perturbation of the current field does result and this complication of the experiment is best avoided. The plastic fixation plate is much more compliant than an equivalent metal plate, but provides adequate stability when used with the external support of a cast, maintaining anatomical opposition while the cast holds alignment. Indeed the overall results of the repaired osteotomy are so good that this method of fixation may merit further study.

The results of our study indicate that electromagnetically induced current had no discernible effect on union as assessed clinically and radiographically. Examination of the final radiographs, with good agreement between independent assessors, disclosed no noticeable difference between treated and control groups. Histology, including quantified measurements, also showed no significant differences. As regards the maximum instantaneous extraction, the mean values for treated and control animals differed only slightly, by about one third of the standard deviation established by the individual measurements. This is too small a difference to be significant. The uptake of the bone-seeking mineral 99mTc-MDP showed marginally significant differences (P < 0.05 at best). Short-term uptake, up to one hour after injection, showed a steady upward trend in both control and treated groups in the five weeks after osteotomy but, in the treated animals, there was more rapid progress towards the final pattern seen at the healed osteotomy site.

Increased mineral uptake is commonly seen in a variety of disorders involving increased skeletal blood flow. Genant et al. (1974) concluded that the short-term uptake was closely correlated with bone blood flow, although Garnett et al. (1975) claimed that more efficient extraction played some part. Our results do not show an increase in extraction in either the control or treated bones. Hughes et al. (1979) have shown that the extraction of strontium by the canine tibia at 2 and 12 weeks after fracture showed no increase despite the considerable increase of blood flow which is known to take place (Paradis and Kelly 1975). Our measurements of uptake and extraction are not, therefore, incompatible and could be explained by increased blood flow at the osteotomy site in the early stages of healing in animals having electromagnetic treatment. Such a conclusion must be treated with extreme caution, because of the marginal significance of the results. Our experimental series indicates that, for this degree of bone injury, the effect of electromagnetic treatment is either absent or very small and is not detectable by clinical, radiographic or histological assessment or by differences in mineral extraction.

It may be that a more clearly differentiated response would be obtained if greater damage had been done to the bone giving less prospect of prompt healing with or without electromagnetic therapy and closer correspondence to established clinical non-union. This view is at present entirely speculative.

Of all the modes of assessment used, only the measurements of mineral uptake showed any significance. Future experiments, which will involve larger groups of animals, will focus on this measurement while the techniques of measurement will be improved where possible.

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