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Electrical Stimulation of the Growth Plate: A Potential Approach to an Epiphysiodesis

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Epiphysiodesis is an operative procedure that induces bony bridges to form across a growth plate of a bone to stop longitudinal growth. This is a very common orthopedic procedure to correct disproportional long-bone growth discrepancies; however, present techniques require an operation and anesthesia. Our study was designed to develop a minimally invasive method of epiphysiodesis by using electrical stimulation with DC current. In a rabbit model, a thin titanium electrode was inserted into a single location of the distal femoral growth plate in three groups: one without current (control), one group with a constant 10 μA (low current, LC), and one group with a 50 μA (high current, HC). The current was delivered for 2 weeks. The nontreated femur served as a control for each animal. Femur lengths were measured and comparisons were made between operated (left) and nonoperated (right) femurs. Digitized histomorphometric and volumetric analyses were performed on each growth plate, and detailed assessments were made of any morphological changes. Using length measurements, the difference in femur length was significantly larger in the HC group and not in the LC or control groups, showing bone growth inhibition at the higher current. In the HC group, bony bridges and disorganized growth plates were observed. This study shows that delivery of an electrical current of 50 μA for as little as 2 weeks can markedly affect bone growth as evidenced by changes in epiphyseal plate volume and architectural organization, and the study supports the use of this minimally invasive approach as a potential method of achieving an epiphysiodesis. Bioelectromagnetics 28:463–470, 2007.

Key words: bone; cartilage; limb-length discrepancies; animal model of epiphysiodesis

INTRODUCTION

Epiphysiodesis is a common orthopedic procedure used to stop growth in a selected growth plate of a long bone [Stephens et al., 1978; Stanitski, 1999]. This procedure is very effective in correcting mild limb-length inequality in children by inhibiting growth in the longer limb [Dahl, 1996]. The first description of an epiphysiodesis technique was reported by Phemister [1933] more than 70 years ago. With the Phemister technique, incisions of about 2″ are placed medially and laterally on the involved extremity in the area of the growth plate. The growth plate is operatively exposed and destroyed at its peripheral margins so that bony bridges form across the growth plate and inhibit longitudinal growth. This operation has an excellent success rate and became a standard of care in treating minor limb-length discrepancies for approximately 25 years. In the late 1970s and early 1980s, percutaneous methods of epiphysiodesis were developed [Bowen and Johnson, 1984]. The percutaneous techniques involve small incisions in which radiographic image intensification is used to guide ablation of the selected growth plate. Other approaches include stapling, an operative procedure to limit growth in a selected growth plate. In this stapling procedure, metallic staples are placed across the growth plate to temporally inhibit longitudinal growth, and, after the desired growth inhibition is achieved, the staples may be removed to allow growth resumption [May and

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Clements, 1965; Frantz, 1971]. All of these techniques have the disadvantages of an operative procedure including anesthesia risk, intraoperative risk, postoperative complications, and high cost. The potential advantage of this newly proposed method over most existing methods is that once developed, it could be implanted using image enhancement through a small incision with local anesthesia. The electrode could be placed percutaneously, and the power source would remain on the dermis. This procedure would reduce all the standard risks of surgical procedures done under general anesthesia. The time required to perform this procedure would be greatly reduced, and it could likely be done as an outpatient. Some risks of infection are still present but could be minimized with precautions that are commonly taken with all orthopedic procedures with external fixators and pins.

Direct current (DC) bone growth stimulators have been used for at least 30 years to stimulate bone formation in spine fusions, fractures, and pseudarthrosis (an area of bone that fails to heal) [Goh et al., 1988; Brighton et al., 1995]. DC stimulators enhance bone formation in the vicinity of the electronegative cathode, which is placed in the fusion mass or at the fracture site. The optimal current range for DC stimulators to induce new bone formation is in the range of 10–50 μA depending on cathode length and material and anatomical placement site [Bozic et al., 1999; Dejardin et al., 2001; France et al., 2001]. There has been no reported change in the growth plate of children when DC electrical stimulators of 20 μA are applied for the purposes of fracture healing or bone fusion. The rationale for using the electrode device included the fact that titanium electrodes pass higher currents than stainless steel without causing tissue necrosis, and that this cathode material is the material currently used in an FDA-approved implantable bone growth stimulator. To be as clinically relevant as possible in this animal model, we also used constant current because it is the component of the only implantable device approved by the FDA.

On the basis of the known bone-forming capacity of electrical current, we postulated that elevation of the electrical current could result in formation of bone bridges across the growth plate cartilage and affect an epiphysiodesis. We theorized that increasing the current several fold would result in exuberant bone formation, potentially causing the closure of the growth plate or necrosis, which would result in the arresting of growth. The purpose of this study was to develop a simple and reliable method of arresting bone growth that could be used to achieve an epiphysiodesis; we believe this can be achieved through growth plate/bone electrical stimulation.

MATERIALS AND METHODS

Animal Model

The study was approved by the Institutional Animal Care and Use Committee and conducted in compliance with all the relevant safeguards and adherence to the Institutional Animal Care and Use Committee-approved protocol. This study was designed to produce a rabbit model for epiphysiodesis of the left femur using a percutaneously implantable electrode in the distal femoral physis (Fig. 1) and electrical stimulation to produce physeal closure. We had three groups of animals (four New Zealand white rabbits of 10 weeks of age for each group): a control group that underwent a sham operation implanted with an inactive electrode, a low-current (LC) group implanted with a 10-μA stimulator, and a high-current (HC) group implanted with a 50-μA stimulator. Each device was secured internally with suture to the fascia, with particular attention to securing the electrode at the point of exit and to the wire to the power source.

Electrical Current Delivery Device

The constant-current delivery system consisted of an implantable generator, which housed the battery and electronics and served as the anode, connected via an insulated lead to a thin titanium cathode. The device was an electrical bone-growth stimulator that is currently available for clinical use (Osteogen, EBI, Parsippany, NJ) that was modified and tested by the company for this study. The cathode consists of a triple-stranded, pure titanium wire with a diameter of 0.5 mm. The electrical stimulator delivered a constant current of either 10 or 50 μA during the 2 weeks. The amplitude of current was confirmed using an implant tester, which measured an RF signal produced by the implanted generator whose frequency was proportional to the in vivo current. A previous animal study determined that the cathode–anode potential required to deliver 50 μA in this model was 2.2–2.4 V.

Surgical Technique and Postoperative Care

After a preanesthetic injection of xylazine (4 mg/kg IM) followed 10 min later with ketamine (50 mg/kg IM), the electrical stimulation device was implanted. Under image intensifier control, a fine needle (24 G) was directed from laterally to medially for a depth of 10 mm into the distal femoral physis, and the needle was withdrawn. Then, a fine wire electrode was placed tightly into the ''needle tract'' from laterally to medially in the distal femoral physis of the left lower extremity. The electrode wire was connected to the electrode stimulation package, which was placed subcutaneously on the upper thigh and buttock. The surgical wound was

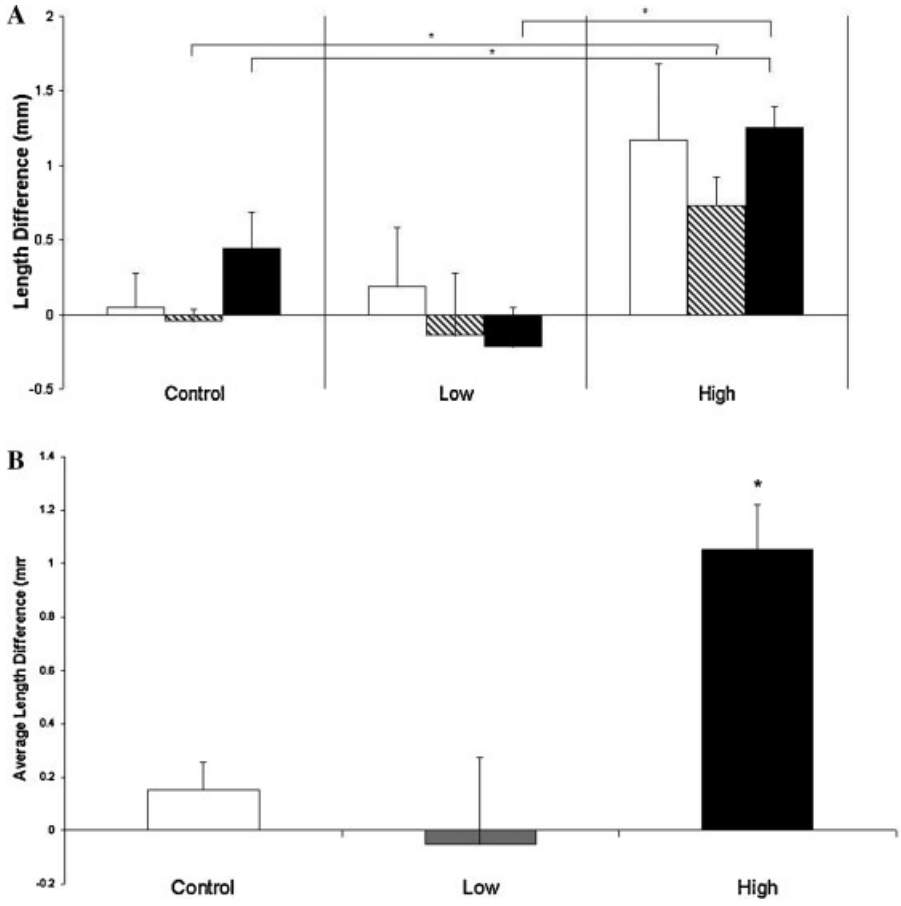

Fig. 1. **Panel A** shows the difference between the length of the right (nonoperated) and the left (operated) femurs of the three treatment groups. The length of the femurs was measured at three anatomical areas including medial, middle, and lateral areas. The difference in femoral lengths was larger in the high-current group (50 μA, High) when compared with the control and low-current groups (10 μA, Low). Data are presented as mean and SEM ($n = 4$); high versus control or low group are significantly different where indicated (*) $P \geq 0.05$. **Panel B** represents the average difference of all three anatomical points presented in distance (mm). Data are presented as mean and SEM ($n = 4$); high versus control or low group are significantly different where indicated (*) $P \geq 0.05$ determined by ANOVA.

closed with absorbable sutures and dressed with sterile iodine. After surgery, the rabbits were housed in an approved animal facility, where all three groups were given identical diet and water supplies. On the 14th day, the animals were euthanized using a commercial veterinary euthanasia product (Sleepaway®, 0.4 ml/lb IM; Ft. Dodge Laboratories, Inc., Ft. Dodge, Iowa).

Macroscopic Studies

After the animals were euthanized, both the right (nonoperated) and the left (operated) femurs were extracted and cleared of ligaments or muscles. Femur lengths were measured with electronic digital calipers at the medial (femoral head to medial condyle), middle (piriformis fossa to intercondylar notch), and lateral (the tip of greater trochanter to lateral femoral condyle) areas. Each measurement was taken three times and averaged. The difference (i.e., change) in length between the right (nonoperated) and left (operated) femurs in each group was plotted as was the average growth in length from combined measurements for each group. Student's *t*-test was performed on the data, and significance was assessed comparing treatment groups.

Anteroposterior and lateral radiographs were obtained, and the findings in the electrode-inserted area and growth plate were described.

Histologic Studies

All specimens were fixed in formalin (10% neutral buffered formalin), and decalcification was performed with ethylenediaminetetraacetic acid (EDTA) using the following solution: 37.22 g of EDTA was dissolved in 1 L of distilled water, then 70 ml of a concentrated hydrochloric acid (HCl) was added. Histological sections of 4 μm in an anterior to posterior sagittal direction of the distal femur were stained with H&E. To

reduce the variance in histological sections, similar regions of the growth plate from both the medial and lateral undulated ridges were evaluated. We studied the narrowing of the growth plate and its possible closure, bony bridges, and the regular or irregular cellular arrangement of various layers in the growth plate. We performed histology on all animals in each group (four), and three sections of each were analyzed.

Histomorphometric Studies

Histomorphometric analysis of the dimensions of the growth plate was done with a Spot CCD camera and microscope integrated with image analysis software (Image Pro Plus 4.5®, Media Cybernetics, Yorktown, VA). Equivalent areas from digital micrographs stained with H&E in full size at a magnification of 10× were analyzed. Each zone was delineated and the analysis was performed on the outlined region of interest (each resting, proliferative, and hypertrophic zones). The area was determined using analysis tools within the program to capture all the stained region. The data collected are given in pixel area, and the results are obtained by comparing the difference in each group and each side (operated and unoperated). This analysis was performed on three sections of each animal and was done blindly without knowledge of group assignment.

RESULTS

Macroscopic Results

Gross examination of the femurs showed extra bone formation at the supracondylar region of the lateral side of the left femurs in the HC group; however, no extra bone formation was seen in the left femurs of the control or LC groups. Also, in all three groups, the fine wire electrodes were appropriately placed and there were no signs of infection.

The difference between the length of the right (nonoperated) and the left (operated) femurs of the three treatment groups was consistently larger in the HC group than in the control and LC groups, which demonstrates a retardation of growth in the HC group (Fig. 1). This retardation of growth was more than twofold (200%) in comparison with the control and the LC groups. There was no difference in growth between the control and the LC groups. Comparison of the difference between the right (nonoperated) and the left (operated) femurs at the three different anatomical locations showed that the area of the physis near the electrode had the greatest inhibition of growth. Statistical analysis of the data demonstrates significance ($P \geq 0.05$) in the comparison of the high versus control or the high versus the low group except with the comparison between the medial measurements. This was due to the variation of the small sample size; however, the trend for a marked inhibition of growth in the high group could be seen in Figure 1B when the three measurements were combined.

Radiographs of the femoral specimens before decalcification showed a large amount of new bone formation at the site of electrode insertion in the HC group and a small amount in the LC group (Fig. 2). No new bone formation was seen at the electrode insertion site in the control group. There were no radiographic differences observed in the growth plates or the medullary bone between the three groups. These radiographic findings were consistent with the observations of the gross specimens.

Microscopic Results

The most obvious histological finding was the appearance of bony bridges and distorted internal structure (fissuring) of the growth plate in the HC group (Fig. 3). The HC group also showed disorganized columnar arrangement of the cartilage cells. We could not detect bony bridges or the same degree of disorganization in the LC or control groups as in the HC group. The resting and proliferative zones of the growth plate in the HC group were of less height than in the LC or control groups. The resting zone showed irregularity of the cells compared with the LC or control groups. No cellular necrosis was observed in any group. The zone of Ranvier of the HC group had an increased number of hypertrophic cells close to the electrode, but only a few hypertrophic cells were observed in the other groups (Fig. 4).

Histomorphometric Results

Histomorphometric measurements showed that the overall height of the growth plate was shortened in the HC and LC groups compared with the control group (Figs. 5 and 6). In the HC group, the area of the whole growth plate, the resting and proliferative zones, and the hypertrophic zone to a lesser extent, were smaller than those of the other groups (control or LC). The ratio (operated femur/nonoperated femur) shows the most shrinkage in the dimensions of resting and proliferative zones. While there is a consistent decrease in all the zones of the growth plate dimensions as a result of 50 mA, performing an ANOVA with a limited sample size ($n = 4$) was not sufficient to achieve statistical significance. There appears to be an electrical dose response, with the HC group having the greatest response and the LC group having a lesser response. These findings were more prominent on the lateral side of the growth plate that was near the side of the electrode than that of the medial side. Also, in the LC group, the dimensions of each zone were smaller than

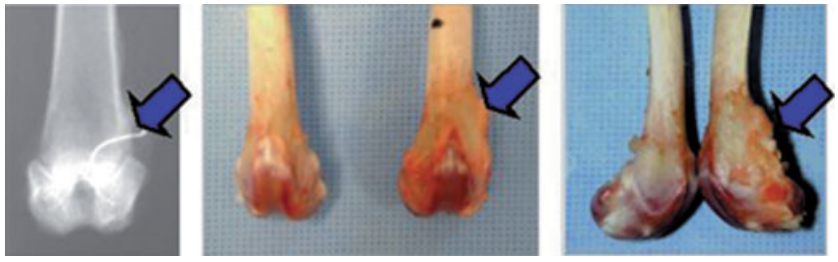

Fig. 2. Photographs and radiograph of the femur. The radiograph of the femur in the high-current group (**left**) shows bone formation at the electrode-implanted area; the electrode is placed appropriately and the growth plate appears to be normal. Gross inspection of the femur in the high-current group (**right**) also shows extra bone formation on the supracondylar area of the lateral side and no bone formation in the control group (**middle**).

those of the control group (Fig. 6). While the results were consistent within each group and the inhibition reliably determined within the zones as described, the limited number of animals tested did not result in enough data for the HC group to achieve statistical significance.

DISCUSSION

The effects of DC electrical stimulation for bone healing have been extensively studied, and it is currently an approved method of treatment in patients undergoing spinal fusions or for treatment of nonunions; however, the effects of stimulation on the growth plate are less well understood [Sato and Akai, 1990]. We focused on the growth plate as a target for the effects of electrical current since it is such a dynamic structure and is made of subsections each with various roles in growth and bone elongation [Abad et al., 2002]. Electrical stimulation for use in bony injuries gained attention in the 1950s when Yasuda began to publish reports on the piezoelectric effects of bone [Yasuda, 1953; Yasuda et al., 1955]. It has been widely studied with regard to its effect on bone healing and has an established role in the treatment of long-bone nonunions and spinal fusions [Brighton et al., 1995]. Direct electrical current on growth cartilage has also been studied, and growth could be altered by varying the amount of electrical current [Armstrong and Brighton, 1986; Okihana and Shimomura, 1988; Sato and Akai, 1990]. The thickening of the growth plate in a rabbit model demonstrated accumulation of hypertrophic cells in the group stimulated with under 8 μA for 2 weeks. Forgon et al. [1985] also reported the stimulation of growth with an electrical current of 20 μA. A number of different approaches have been used to achieve an epiphysiodesis, including electrocautery [Rosen et al., 1990] or lasers [Morein et al., 1978] to destroy cells of the growth plate. In our study, we show evidence of growth retardation or partial epiphysiodesis using a level of electrical current of 50 μA applied directly to the epiphyseal plate. This growth retardation was observed with 50 μA but not with 10 μA or the electrode alone, and this was similar to the retardation reported from other operative epiphysiodesis methods

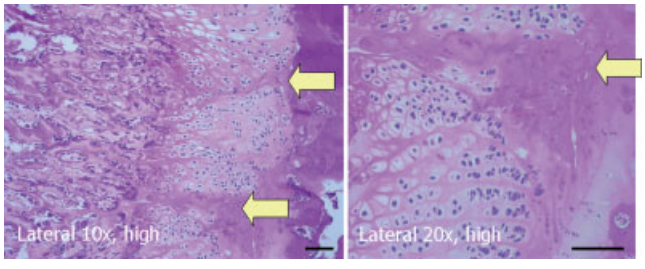

Fig. 3. Photomicrograph of representative growth plate of the high-current group showing the distorted cellular columnization, fissuring, and an area of bone bridge formation (**left**, original magnification 10×). Higher magnification shows the extent of the cellular distortion (**right**, original magnification 20×). Bars = 50 μM.

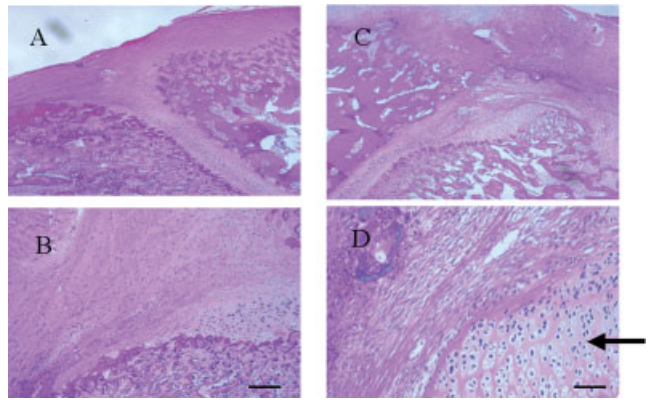

Fig. 4. Photomicrograph of a representative zone of Ranvier. The number of hypertrophic cells was noticeably increased in the high-current group (HC, **C**,**D**) compared with the control group (CTL, **A**,**B**). **Top panels** are low power (original magnification 4×); **bottom panels** are original magnification 10×. Arrow indicates typical area with increase in hypertrophic-appearing cells. Bars in B and D = 50 μM.

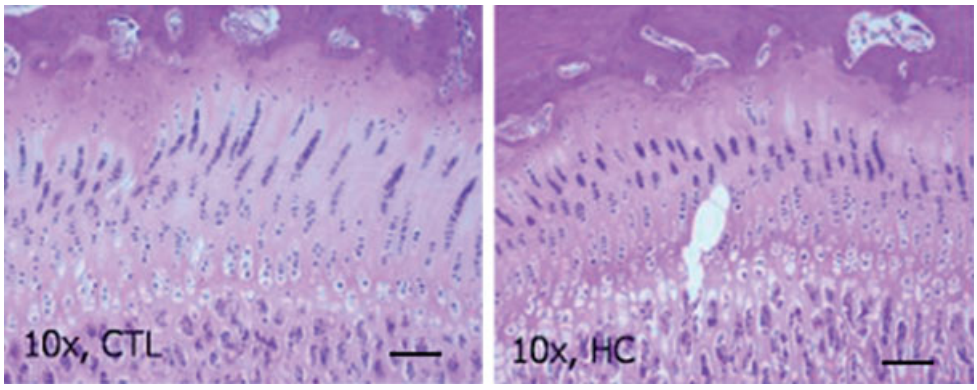

Fig. 5. Photomicrographs of the growth plates of the control group (CTL, **left**) and the high-current group (HC, **right**). The width of the total growth plate as shown here was smaller in the HC group than the control group. Bars = 50 μM.

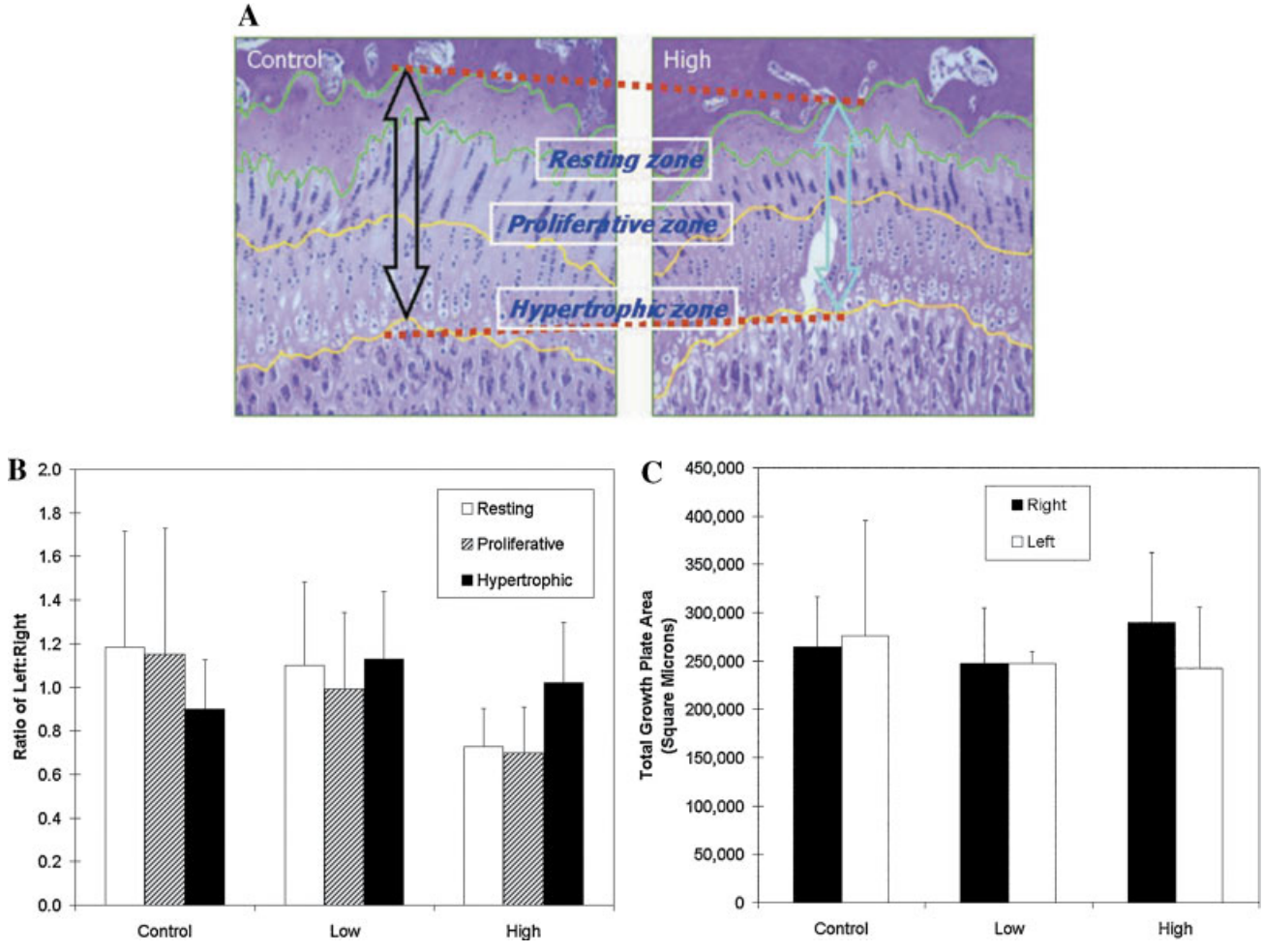

Fig. 6. Zonal changes in growth plates in control, low-current, and high-current groups. **A**: Example of how the zones were delineated. **B**: The ratio of left to right femur (stimulated: no treatment) within the three growth plate zones comparing treatment to the sham control (no current), and (**C**) the area of the combined zones of the growth plate. The data presented are from the lateral portion of the growth plate. The area is in square microns and shown as the mean of all four animals. Data were collected from digitized images and as described in the Materials and Methods Section. The boundaries of each zone were delineated using the right and left edge of the image view as the boundary, and the distal and proximal margins based on cell and matrix characteristics. The mean and SD of three sections analyzed are presented. The ratio (operated femur/non-operated femur) shows the most shrinkage of the dimensions of resting zone and proliferative zones. While there is a consistent decrease in all the zones of the growth plate dimensions as a result of 50 μA, performing an ANOVA with a limited sample size ($n = 4$) was not sufficient to achieve statistical significance.

[Morein et al., 1978; Rosen et al., 1990]. In this study, our histology was consistent with the findings of shrinkage of the growth plate with distinct morphological changes such as local clusters of chondrocytes and loss of columnar arrangement, which were similar to findings in epiphyseal stapling [Karbowski et al., 1989]. In an in vitro study, Okihana and Shimomura [1988] reported the devitalization of cells with DC over 10 μA; however, in this study with rabbits, there was no devitalization at the cellular level. The currents used in this study are similar to those described previously in a rabbit tibia model in which a 1-cm stainless steel cathode was placed in the medullary canal [Brighton et al., 1981]. In that study, bone formation around the cathode was optimal at 20 μA, but tissue necrosis occurred at higher currents up to 50 μA. The necrosis was due to the HC density, electrode potential, and resulting hydrolysis that occurs over a small region between the cathode and the insulation. This occurs in response to the formation of an insulating protein layer that forms over the bare stainless steel cathode in vivo. It has been previously shown that this effect does not occur with titanium cathodes, which distribute current uniformly over their surface using 50 μA [Dejardin et al., 2001] nor in another study using 100 μA [Toth et al., 2000]. Thus, in our study, 50 μA was expected to produce changes in bone formation without concomitant necrosis and there was no evidence of necrosis found.

Gross measurements and histomorphometry are methods that have been used in multiple articles to verify growth plate function or inhibition. In this study, gross measurements of the femoral length demonstrated restricted growth in the HC group, which is evidence of growth inhibition. Histomorphometry is reported also to be an accurate study to confirm delayed growth [Weise et al., 2001], and the measurement of the height of the growth plate or individual cell layer is a good quantitative method [Glickman et al., 2000; Arriola et al., 2001]. Shrinkage of dimension in the whole growth plate was observed in the HC group in this study. The dimension of the zones within the growth plate was comparable between the groups in our study. We observed a decrease in the volume of the resting zone in the HC group in comparison with the other groups. Glickman et al. reported difficulty in determining an accurate border between the proliferative and hypertrophic zones, and, for this reason, we combined the two zones into one dimension for measurement. This measurement was decreased in the HC group compared with the other groups, which is evidence of growth inhibition. Our study cannot rule out the possibility that the growth plate at the proximal end of the femur could have affected the results. In fact, in one possible scenario, the electrical stimulation may have had an even greater effect than our data demonstrate due to the compensatory growth at the growth plates at the proximal end as a result of decreased growth velocity at the distal (experimental) femoral growth plate.

Electrical stimulation has been widely studied with regard to its effect on bone healing and has an established role in the treatment of long-bone nonunions. It has been reported that a constant current of 20 μA resulted in the greatest amount of bone formation with no signs of necrosis, but a higher current showed the changes of cellular necrosis or destruction [Brighton et al., 1995]. More recent studies with titanium electrodes rather than the stainless steel electrodes used by Brighton demonstrated that new bone formation occurred without necrosis with currents up to 50 μA [Bozic et al., 1999; Dejardin et al., 2001]. We also could observe a large amount of newly formed bone on the area of the electrode in the 50 μA group, but signs of necrosis of bone were not seen. In the HC group, bone bridges that crossed the growth plate were found. Based on preclinical and clinical experiences with devices such as those used in our model, they will not produce any thermal changes around the electrode, thus the potential pathways that may be affected promoting changes in bone growth are likely through mechanisms such as the promotion of cell differentiation and/or growth factor and cytokine production.

Our data support the hypothesis that fine wire electrodes with increased current above that used for bone healing can cause premature closure of the growth plates, resulting in an epiphysiodesis. Hypothetically, a percutaneously implantable electrode could be placed under local anesthesia and fluoroscopic guidance, thereby reducing the cost of operative procedures and the risk of general anesthesia. Also, for clinical applications, a percutaneously implantable electrode would cause minimal soft tissue injury and would not weaken the bone as is currently seen from a surgical epiphysiodesis. The electrical generator could be externally attached to the electrodes.

SUMMARY

These data support the idea that an epiphysiodesis could be achieved by electrical stimulation of the growth plate. Electrical current made a marked change in the growth plate volume and characteristics in this rabbit model. Interestingly, the results demonstrated that after just 2 weeks of electrical treatment, the physical length could be measured as arrested in the HC group (50 μA). Results were reproducible and consistent between physical length measurements and morphometric analyses. Our findings support the use of

electrical current to arrest growth and produce bony bridges across the growth plate in long bones with potential to achieve an epiphysiodesis.

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