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Acceleration of Tibia and Distal Radius Fracture Healing in Patients Who Smoke

[Original Articles: Fractures]

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Outline

Graphics

Abstract^

A low intensity ultrasound device was investigated as an accelerator of cortical and cancellous bone fracture healing in smokers and non-smokers. Statistically significant reductions in healing time for smokers and nonsmokers were observed for tibial and distal radius fractures treated with an active ultrasound device compared with a placebo control device. The healing time for a tibial fracture was reduced 41% in smokers and 26% in nonsmokers with the active ultrasound device. Similarly, distal radius fracture healing time was reduced by 51% in smokers and 34% in nonsmokers with the active device. Treatment with the active ultrasound device also substantially reduced the incidence of tibial delayed unions in smokers and nonsmokers. The use of the active ultrasound device accelerates cortical and cancellous bone fracture healing, substantially mitigates the delayed healing effects of smoking, speeds the return to normal activity, and reduces the long-term complication of delayed union.

Despite known risks and warnings, an estimated 52.4 million Americans are regular cigarette smokers consuming approximately 800 billion cigarettes annually.[26] The most prevalent of the many diseases related to smoking are lung cancer, coronary heart disease, and chronic obstructive pulmonary disease. More than 4000 compounds have been isolated from cigarette smoke with nicotine, carbon monoxide, and hydrogen cyanide among the many cited to have adverse physiologic effects.[26] Smoking increases heart rate, total peripheral resistance, blood pressure, and coronary blood flow.[1,7,12,15,21] Patients who smoke have a higher incidence of vasoocclusion after surgery, a higher failure rate of skin flaps and arteriovenous shunts, more arterial insufficiency, and a greater chance of recurrence of carotid stenosis.[17,20] Smoking a single cigarette has been shown to reduce digital blood flow.[25]

Cigarette smoking also has a profound effect on bone and bone healing. Post-menopausal women who smoke lose more cortical bone and have more spinal osteoporosis than do nonsmokers.[5] The risk of fractures is 2 to 6 times higher in patients who smoke because of reduced bone density.[19] Pseudarthrosis after spinal fusion occurs at least 4 times more often in patients who smoke compared with patients who do not smoke.[2,3,9] Similar findings have been reported after ankle arthrodesis.[4] Nicotine in smoke inhibits the revascularization of bone grafts and may be responsible for the high pseudarthrosis rate.[5] Delayed healing and nonunion of tibial shaft and mandibular fractures also occur more frequently in patients who smoke.[10,16]

Low intensity pulsed ultrasound has been reported to accelerate the normal fracture repair process in animals and humans.[6,13,18,29] A significant increase in fracture callus amount and fracture stiffness and strength was found for rat femoral fractures treated with low intensity ultrasound.[28,30] In the early healing phase, low intensity ultrasound increased soft callus, altered expression of cartilage related protein, and increased aggrecan expression.[30] Xavier and Duarte [29] have reported clinical data on the acceleration of fracture healing with low intensity ultrasound and on the successful treatment of ununited diaphyseal fractures in pseudarthroses.

In a Food and Drug Administration approved premarket approval multicenter, prospective, randomized, double blind, and placebo controlled clinical trial of a low intensity ultrasound device (Sonic Accelerated Fracture Healing System, Exogen, Piscataway, NJ), a statistically significant decrease in healing time was reported for cortical bone (tibial shaft) fractures (active device, 96 days; placebo device, 154 days [$p < 0.0001$]).[11] In addition, the 36% incidence of delayed union in the placebo group was significantly reduced ($p < 0.003$) with active ultrasound treatment where only a 6% incidence of delayed union was observed. Similar findings were reported in a second clinical trial for cancellous bone (posterior displaced distal radius or Colles') fractures(active device, 61 days; placebo device, 98 days [$p < 0.0001$]).[14] The purpose of this study was to compare in smokers and nonsmokers the clinical and radiographic healing time of cortical and cancellous bone fractures treated with the ultrasound device in the above clinical studies.

MATERIALS AND METHODS^

All patients presenting who satisfied the inclusion and exclusion criteria were given the opportunity to participate. Patients who agreed to participate and provided written informed consent were entered consecutively into the studies and received either an active or a placebo device according to a computer generated randomization code. The code was broken only after all clinical and radiographic review was completed. Smoking status during and before the study was documented prospectively for 50% of the patients with a tibial fracture and retrospectively for the remaining 50% of the patients with a tibial fracture and for the patients with a distal radius fracture. All patients were asked whether they had ever smoked cigarettes and, if so, the number of years they had smoked, the number of packs smoked per day, and whether they had smoked during their participation in the fracture studies. If they had smoked previously but quit or stopped during the fracture study, they were asked the year they stopped smoking, the number of years they had smoked, and the number of packs of cigarettes smoked per day. All data were first evaluated comparing smokers (those who smoked during their fracture treatment) versus nonsmokers (those who did not smoke during their fracture treatment). In addition, to study smoking history effects, patients who had a history of smoking in the previous 10 years were combined with those who smoked during their fracture treatment and were compared with patients with no history of smoking and those who quit smoking for more than 10 years before their fracture treatment.

Tibial Shaft Fractures^

Skeletally mature men and nonpregnant women who had a closed or Grade I open tibial diaphyseal fracture that was primarily transverse, short oblique, or short spiral and that could be treated effectively with closed reduction and immobilization in a cast were eligible for inclusion in the study. Patients excluded were those in whom either the prereduction or postreduction anteroposterior (AP) or the lateral radiographs showed that the length of the fracture line was more than twice the diameter of the diaphyseal shaft (a long spiral or long oblique fracture), the postreduction displacement was more than 50% of the width of the shaft, or the postreduction fracture gap averaged more than 0.5 cm. Other exclusion criteria were open fractures, except Grade I as defined by Gustilo and Anderson [8]; fractures of the tibial metaphysis; fractures with persistent shortening of more than 1 cm after reduction; fractures that were not sufficiently stable for treatment with immobilization in an above the knee cast; fractures with a large butterfly fragment (larger than 2 times the diameter of the tibial shaft); pathologic fractures; and comminuted fractures(comminution with fragments of less than 1 cm in length was acceptable). Patients also were excluded if they were receiving steroids, anticoagulants, prescription nonsteroidal antiinflammatory medication, calcium channel blockers, or diphosphonate therapy; had a history of thrombophlebitis or vascular insufficiency; or had a recent history of alcoholism or nutritional deficiency, or both.

Sixty-seven patients with fractures (33 that were treated with an active unit and 34 that were treated with a placebo unit) complied with the protocol and, therefore, represented the core group of fractures that were analyzed for inferences regarding device safety and effectiveness. Men constituted 25(76%) of 33 of the active group and 28 (85%) of 34 of the placebo group. The average age of the active group was 36 years as compared with 31 years for the placebo group. There were 64 closed fractures (31 in the active treatment group and 33 in the placebo treatment group) and 3 Grade I open fractures (2 in the active treatment group and 1 in the placebo treatment group). The randomization process produced comparable active and placebo treatment groups in all smoking strata.

The fractures were treated conventionally with closed reduction and immobilization in an above the knee cast. The 3 Grade I open fractures were treated with initial debridement, and the wounds were allowed to heal by secondary intention. A retaining and alignment fixture made of molded plastic was inserted into a window centered over the anteromedial surface of the cast at the site of the tibial fracture. This fixture held the treatment head module in place. Treatment was started within 7 days after the fracture and consisted of a 20-minute period each day. A warning signal was sounded by the main operating unit if there was not proper coupling of the treatment head module to the skin. A visual and audible signal alerted the patient that the treatment was complete. The patient's compliance with instructions for use of the device was measured by a timer inside the main operating unit, and a patient maintained daily treatment log. The active and placebo devices were identical in every way (they had the same visual, tactile, and auditory signals), except only active devices emitted an ultrasound signal. Treatment was continued for 20 weeks or until the fracture was healed sufficiently to discontinue the active or the placebo ultrasound therapy.

The ultrasonic treatment head module delivered an ultrasound pressure wave signal that was composed of a burst width of 200 microseconds containing 1.5 MHz sine waves, with a repetition rate of 1 kHz. The intensity of the pressure wave applied to the skin at the fracture site was 30 mW/cm^2.

All patients were scheduled to return for followup AP and lateral radiographs at 4, 6, 8, 10, 12, 14, 20, 33, and 52 weeks after the fracture. Clinical followup evaluations were performed at the time of any cast change(usually at 6 and 10 weeks) and at the followup visit when radiographic evaluation indicated that the fracture had healed sufficiently to allow removal of the cast. The end point of the study was a healed fracture, as judged on clinical examination (fracture stable with no pain on manual stress) and on radiographic assessment (3 of 4 cortices bridged); fractures that were not healed at 150 days postfracture were defined as delayed unions. All radiographic healing assessments were performed in a masked manner by the study principal investigator (JDH).

Distal Radius (Colles' Fractures)^

Patients included in this study were men and nonpregnant women 20 years of age or older with acute closed fractures of the distal radius (Colles'). These fractures primarily followed the classical definition of Colles' and were defined as predominantly transverse fractures of the distal radius within 4 cm of the tip of the radial styloid with dorsal angulation. Intraarticular involvement of the radiocarpal or radioulnar joint or both was acceptable. Fractures with a coincidental fracture of the ulnar styloid also were acceptable. Closed reduction and a standard cast immobilization technique were mandatory. All fractures were required to be satisfactorily reduced based on radial height, radial angle, and dorsal tilt criteria.

Patients excluded were those with other types of distal radius fractures(Chauffeur's, Barton, and Smith's). Fractures with associated fractures of the ulnar shaft and patients with fractures requiring surgical intervention were excluded. Patients receiving steroids, anticoagulant therapy, those with a history of thrombophlebitis, or vascular insufficiency involving the upper extremity, and those with nutritional deficiency or alcohol dependence also were excluded.

The ultrasound devices used in this study were identical to those used in the tibial study and imparted the same ultrasound pressure wave signal. Again, the placebo devices had disconnected ultrasound transducers and emanated no ultrasound pressure wave. They were identical in all operations and visual and audible characteristics to the active units.

After adequate reduction, the fractures were immobilized in a short arm cast with the wrist in slight volar flexion and ulnar deviation. Using a template, a cast window was created on the dorsal aspect of the cast over the fracture site, and an alignment fixture was secured in the cast window with plaster. This fixture held the ultrasound treatment head module in place during the daily 20-minute treatments. All patients started ultrasound treatment within 7 days of the fracture data and were instructed to use their assigned device for 1 continuous 20-minute treatment per day until the 10-week postfracture followup visit. Anteroposterior and lateral radiographs were taken of all patients at time of injury, postreduction, and at all followup visits. The protocol called for a first cast change at 3 weeks so that cast free radiographs could be taken and the fracture could be palpated and stressed for indications of clinical stability. Patients were scheduled to return for clinical and radiographic followup evaluation at 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16 weeks postfracture.

Sixty-one fractures (30 in the active group and 31 in the placebo group) complied with the protocol and, therefore, represented the core group of fractures that were analyzed for inferences regarding device safety and effectiveness. Women constituted 24 (80%) of 30 of the active group and 27(87%) of 31 of the placebo group. The average age of the active patients was 54 years and the placebo group averaged 58 years. Displaced fractures comprised 40% of the active group and 45% of the placebo group. The ulnar styloid was fractures in 67% of the active group and in 58% of the placebo group. Radioulnar joint involvement was noted in 63% of the active group and in 55% of the placebo group. Radiocarpal joint involvement was noted in 50% of the active group and in 32% of the placebo group. Fifty percent of the active group had comminuted fractures, whereas 29% of the placebo group had comminuted fractures. All active group fractures were impacted and 90% of the placebo group fractures were impacted. The mean Frykman score was 5.2 in the active group and 4.4 in the placebo group. The average prereduction radial deviation was 19° in the active group and 18° in the placebo group, with postreduction averages of 20° and 21° in the active and placebo groups, respectively. The average prereduction dorsal tilt was 16° in the active group and 18° in the placebo group with postreduction averages of-0.5° and -1.1° in the active and placebo groups, respectively. The average prereduction radioulnar index was -0.2 mm in the active group and-0.5 mm in the placebo group with postreduction averages of 0.0 mm and -0.1 mm in the active and placebo groups, respectively. Prereduction radial height averaged 8 mm in the active group and 8 mm in the placebo group with postreduction averages of 10 mm in the active and the placebo groups. The randomization process produced comparable active and placebo treatment groups in all smoking strata.

The endpoint of the study was a healed fracture as judged on clinical examination (fracture site was clinically solid and free of tenderness and pain on palpation) and on radiographic assessment. All radiographic healing criteria were performed in a masked manner by the study principal investigator (TKK) based on radiographs from all followup visits for each fracture. Fractures were defined as healed when they were clinically and radiographically (4 of 4 bridged cortices) healed. Cortical bridging was defined as the reestablishment of cortical continuity across the cortical interruption of each cortex. The loss of reduction was determined from initial prereduction and postreduction dorsal tilt values established from the initial radiographs and provided the total reduction at the time of injury. Weekly followup radiographs were assessed for loss of reduction in those fractures with more severe dorsal angulation (at least 10° of prereduction dorsal tilt).

Statistics^

Statistical analyses were performed with the Statistical Analysis System software (SAS Institute, Cary, NC) using the General Linear Models Procedure for Analysis of Variance to contrast the active ultrasound treated versus placebo control group mean time in days postfracture to attain each healed parameter response (or the percentage reduction loss). The statistical model included smoking stratum effect, treatment effect, and smoking stratum by treatment interaction effect. Tables 1 through 4 present within stratum mean ± standard error of the mean and the active versus placebo p values from the analysis of variance and from Satterthwaite's test if variances were unequal (F'-test $p < 0.05$). Fisher's exact test was used to contrast the active ultrasound treated versus placebo control group incidence of delayed union tibial fractures (Table 5).

TABLE 1. Stratification of Patients With a Tibial Fracture Who Smoked During the Study Versus Patients Who Did Not Smoke During the Study (Days Postfracture)

TABLE 2. Stratification of Patients With a Tibia Fracture Who Smoked During the Study or Within 10 Years of the Study Versus Patients Who Never Smoked Or Who Stopped Smoking Greater Than 10 Years Prior (Days Postfracture)

TABLE 3. Stratification of Patients With a Distal Radius Fracture Who Smoked Versus Patients Who Did Not Smoke During the Study (Days Postfracture)

TABLE 4. Stratification of Patients With a Distal Radius Fracture Who Smoked During the Study or Within 10 Years of the Study Versus Patients Who Never Smoked or Who Stopped Smoking Greater Than 10 Years Prior(Days Postfracture)

TABLE 5. Incidence of Tibia Delayed Union Fractures: Percent Delayed Union Fracture Incidence (Number of Delayed Union Fractures/Number of Fractures in Stratum)

RESULTS^

Patient compliance with device usage was excellent and comparable between the active and placebo treatment groups in both studies. There was good agreement of internal device timers and patient logs.

Tibial Shaft Fractures^

Seven of the 67 patients were lost to followup for documentation of smoking status. Table 1 presents results of clinical and radiographic response parameters for smokers and nonsmokers that include complete clinical and radiographic healing (fracture stable with no pain on manual stress and 3 of 4 cortices bridged) and individual clinical and radiographic criteria. Clinical healing was defined as a stable fracture with no pain on manual stress independent of radiographic status. The time to cast removal also is shown and was the time it was thought clinically healing was sufficient to support cast removal.

Patients in the placebo treatment group who were smoking during the study healed slower than did patients who did not smoke (175 days, smokers, versus 129 days, nonsmokers). The healing times for all clinical and radiographic parameters were longer in patients who smoked. (Table 1). The application of low intensity ultrasound was found to have a significant effect on fracture healing time in patients who smoked and patients who did not smoke. Significant reductions in time to healing events were found with the active ultrasound device versus the placebo control group, a 41% reduction in the time to a healed fracture for patients who smoked (175 days for placebo device versus 103 days for active device, $p < 0.006$) and a 26% reduction in healing time for nonsmokers (129 days for placebo device versus 96 days for active device, p <

0.05). There was no statistical difference in the healing time of patients who smoked and patients who did not smoke in the active ultrasound treatment group (103 days active device versus 96 days placebo device).

Results of patients who were smoking during the study combined with those who had smoked within the previous 10 years are compared with results of nonsmokers and those with no history of smoking within the previous 10 years (Table 2). These data showed results similar to the previous analyses with the placebo group of patients who smoked or who had a history of smoking healing slower than did nonsmokers and those that had quit smoking longer than 10 years ago (164 days smoking or history of smoking versus 129 days nonsmoking and no history of smoking). There was no statistical difference in healing time of patients who smoke and patients who do not smoke in the active ultrasound treatment group. Again, the use of the low intensity ultrasound device was found to significantly reduce healing time for all parameters with smokers and those with a history of smoking who healed in only 98 days with the active device versus 164 days with the placebo device (a 40% faster active healing device relative to placebo device, $p < 0.002$).

Table 5 presents results for incidence of tibial delayed union for active treated and placebo control group fractures stratified by smokers and nonsmokers. Active ultrasound treatment was found to reduce the incidence of delayed union in patients who do not smoke (8% active versus 27% placebo). This superiority of active ultrasound treatment in reducing the incidence of delayed union versus placebo also was observed for study smokers with 0% active versus 36% placebo delayed union incidence($p < 0.098$). In addition, for smokers and those with a history of smoking within the past 10 years, a 0% incidence of delayed union was found with the active device versus 33% incidence found with the placebo device ($p < 0.02$).

Distal Radius (Colles' Fractures)^

Ten of the 61 patients could not be located during the retrospective documentation of smoking status. Only 18% of the remaining 51 patients were smoking during this study (Table 3). The use of the ultrasound device was found to significantly reduce the healing time for nonsmokers (66 days active versus 100 days placebo, a 34% faster active healing relative to placebo, $p < 0.0001$) and smokers (48 days active versus 98 days placebo, a 51% faster active healing relative to placebo, $p< 0.003$). Significant reductions in time to healing response for active versus placebo also were found for the individual radiographic healing criteria, including loss of reduction (Table 3). No differences were determined between smokers and nonsmokers in either treatment group for any of the radiographic healing criteria.

Results of patients who were smoking during the study combined with results of patients who smoked within the previous 10 years are compared with results of nonsmokers and the results of those with no history of smoking in the previous 10 years, as listed in Table 4. As was observed in the analysis above and in the tibial study, the use of the ultrasound device was found to significantly reduce the healing time in smokers and those with a history of smoking (51 days active device versus 109 days placebo device, a 53% faster active healing relative to placebo, $p < 0.0002$) and nonsmokers and those with no history of smoking (67 days active device versus 98 days placebo device, a 32% faster active device healing rate relative to placebo device, $p < 0.0001$). Similar reductions were found in nearly all radiographic categories (Table 4).

DISCUSSION^

Cigarette smoking has a profound effect on all types of wound healing. Individually and in combination, the particulate and gaseous compounds found in cigarette smoke undermine the conditions required for expeditious wound repair.[27] The effects of nicotine, carbon monoxide, and hydrogen cyanide combine to cause tissue anoxia, cellular hypoxia, prevention of the proliferation of cells, vasoconstriction, and a decrease in the oxygen carrying capacity of blood. Clinicians should be aware of the effects of smoking when caring for or advising patients who suffer wounds as the result of trauma or disease or who are about to schedule elective procedures.

The results of this investigation are in agreement with the work of Kyro et al [16] and the work of others describing detrimental effects of smoking on bone healing in a variety of sites.[2-5,9,10,19] The healing of tibial fractures in patients who smoke required an average of 175 days compared with 129 days in patients who do not smoke (smokers required 36% longer time to heal) when using the placebo device. There were no statistical differences in time to healing between smokers and nonsmokers treated with the active ultrasound device, indicating the active ultrasound treatment had a positive effect on fracture healing in smokers to significantly decrease the time to healing.

Low intensity ultrasound reduced the time to attain a healed fracture with statistically significant reductions in healing time for smokers and nonsmokers in the tibial and distal radius fracture studies. In fact, the time needed for healing of a tibial fracture in a patient who smoked and was treated with the active ultrasound device was reduced by 72 days or more than 41% shorter than that of a patient who smoked and was treated with a placebo control device. A similar reduction was observed in distal radius fractures. Treatment with low intensity ultrasound also substantially reduced the incidence of tibial delayed unions in smokers and nonsmokers with delayed union occurring in 0% of smokers treated with the active ultrasound device versus more than 36% of smokers in the placebo control group.

The exact mechanism of action of the ultrasound device is unknown. However, studies in animals and humans have shown repeatedly its effectiveness in accelerating the bone repair process.[6,11,13,14,18,28-30] It has been theorized that the ultrasound pressure waves may mediate biologic activity directly by mechanical deformation of the cell membrane or the extracellular matrix or indirectly by an electrical effect caused by cell deformation.[11] Ryaby et al [22-24] showed that low intensity pulsed ultrasound in isolated cell systems produced significant multifunctional effects of direct relevance to bone formation and resorption such as increasing calcium uptake and modulating adenylate cyclase activity, transforming growth factor beta synthesis, bone morphogenic protein effects, and parathyroid hormone response.

It is unquestioned that smoking results in numerous physiologic manifestations including a significant delay in the healing of bone fractures. Clinicians must be aware of this fact and advise patients accordingly. The studies of tibial and distal radius fractures have shown that the use of low intensity pulsed ultrasound accelerates cortical and cancellous bone fracture healing in smokers and nonsmokers, substantially mitigates the delayed healing effects of smoking, speeds the return to normal activity, and reduces the long-term complication of delayed union.

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