ACCELERATION OF OSSEOUS FRACTURE REPAIR BY PULSED LOW-INTENSITY ULTRASOUND THERAPY: A PRELIMINARY STUDY

O. Rodríguez¹, R. Monreal²

¹Ultrasonic Therapy Group, Ultrasound Dpt, Institute of Cybernetic, Mathematics and Physics (ICIMAF), Calle 15 e/ C y D, CP 10400, La Habana, Cuba. Email: reyru@cidet.icmf.inf.cu.
²Hospital “Comandante Manuel Fajardo”, Hospitales y Zapata, CP 10400, La Habana, Cuba. Tel. (537)-55-2448.

ABSTRACT
Low-intensity pulsed ultrasound in the range used in diagnostic applications, has been shown in many clinical studies to be an effective means to accelerate fracture repair. This paper presents the results obtained in a study effected in the hospital “Comandante Manuel Fajardo” in Havana, Cuba, between April 1999 and February 2000 with the use of this technique. A total of twelve ununited fractures, including new fractures, delayed unions and no-unions were treated daily for twenty minutes with a pulsed ultrasound signal of 30 mW/cm² (SATA), and pulse bursts width of 400 µs repeated with a frequency of 0.5 kHz. The treatments were applied until the fractures were clinically and radiographically healed. Many of these patients had multiple attempts to achieve union, which failed. Metal fixation was present in nine of them. Radiographic evidence of healing was the bridging by callus of three cortices, and patients were clinically healed when they could weightbears without pain. None treatment failed.

In addition, it is presented the technical characteristics of the equipment. It is an advanced microprocessor-controlled apparatus, for the generation of therapeutic ultrasound, designed in compliance with the IEC Standards.

Key-words: Ultrasound, Therapy, Fracture-repair, nonunion

1. INTRODUCTION
Ultrasound is an acoustic radiation at frequencies above the limit of the human hearing, i.e., 20 kHz. It is a form of mechanical energy that can be transmitted into the body as high-frequency acoustical pressure waves. The first effect of ultrasound in tissue is micromechanical stress and strains, which can produce several physical [1] [2], biochemical [3] and biological events in tissue [4]. Additionally, the absorption of this type of energy is used by therapeutic ultrasound to increase the temperature of tissue [5]. Nowadays, ultrasound has many medical applications. It is used therapeutically, operatively as well as in diagnostic procedures.

In Physical Therapy and Rehabilitation, usually ultrasonic intensities of one to three W/cm² are used [6]. In operative procedures of ultrasound, intensity levels of five to more than 4000 W/cm² are employed to, among other effects, generate heat, to ablate or even to evaporate tissue [7]. In diagnostic imaging, intensities are much lower, from 0.5 to 50 W/cm², and in practice have no thermal effect [8].

To improve the biological response of bone formation in bone fracture treatment, now osteogenic, osteoconductive, and osteoinductive methods are attempt. Among the methods is the biophysical stimulation, which include mechanical, electric, electromagnetic and ultrasonic stimulation. The promotion of bone formation by means of ultrasound could suggest a relation with the Wolf’s law [9] that postulates that the structure of bone adapts to changes of its mechanical stress environments.

In 1983 Duarte reported in a model of rabbits, that low-intensity pulsed ultrasound can accelerate the healing of the fracture at the site of bilateral osteotomy of fibula and at bilateral drill holes on the cortex of femur, by radiological and histological evaluations, in a placebo controlled study [10].

Xavier and Duarte demonstrated acceleration of normal fracture healing in humans using this technique. They also indicated that low-intensity ultrasound can induce bone repair of ununited diaphyseal fractures [11].

Pilla showed in a controlled rabbit model on midshaft fibular osteotomics and in prospective double-blind, randomized human clinical trials in groups of patients suffering Colles’s and tibia diaphyseal fractures, that low-intensity pulsed ultrasound significantly accelerates fresh fracture repair. In addition, he reported that maximal effects occurs at 30 mW/cm² with an ultrasound signal of 1.5 MHz, 200 µs sine wave burst width, repeating at 1 kHz [12].

Wang et al. [13] reported in highly controlled model of rats on closed femoral shaft fractures, that low-intensity ultrasound stimulation at 0.5 and 1.5 MHz significantly increased the mechanical parameters of the healing fracture callus, when tested to failure in torsion. Moreover, they pointed out that there was not a significant difference in the effects obtained by these two different ultrasound frequencies on the mechanical properties of the callus.
In a multicenter, prospective, randomized, double-blind, placebo-controlled study, Heckman et al. [14] reported a significant acceleration (38% approximately) of fracture healing in patients who received active low-intensity pulsed ultrasound for the treatment of tibia diaphyseal fracture.

In the same manner Kristiensen et al. [15], shown that this type of ultrasound therapy can significantly shortening the time to radiographic healing of dorsally angulated fracture of the distal aspect of the radius that had been treated with manipulation and cast. The time to union was significantly shorter for the fracture that were treated with ultrasound that it was for those that were treated with placebo 63 ± 3 days compared with 98 ± 5 days.

Many others clinical investigations with the use of low-intensity pulsed ultrasound have been shown successful healing of fresh fractures delayed unions and nounions, which include fractures fixed with metallic implants [16]-[25].

Ultrasound therapy of fractures may be more important in some groups of patients, for example in world class athletes, in which a prolonged period of rest must be avoided [26]. Stress fracture typically occurs in normal bone that has been subjected to repeated cyclic loading with loads normally less than those that causes spontaneous fracture. The requirements for constant training in the athlete do not provide sufficient time for the repair process in bone to counteract high forces inflicted by rigorous training regimen.

Taken into account the reported results about the use of low-intensity pulsed ultrasound in the treatment of bone fractures, and the possibility of implementing, for this propose, an equipment for clinical investigation at hospital, the goals of this study were: 1) To use this therapy for patients affected firstly of delayed union and nounions. 2) To evaluate by ourselves, the utility of this technique.

Then, this paper presents the results obtained in a study effected in the hospital “Comandante Manuel Fajardo” in Havana, Cuba, between April 1999 and February 2000 with the use of this technique. In addition, it is presented the technical characteristics of the equipment, which is an advanced microprocessor-controlled apparatus for the generation of therapeutic ultrasound, designed in compliance with the IEC Standards.

2. Materials and Methods

There were a total of twelve patients in the study. All of them were consulted before of the ultrasound applications, obtaining a written permission. The patients were treated daily for twenty minutes with a pulsed ultrasound signal of 30 mW/cm² (SATA) and pulse bursts width of 400 µs repeated with a frequency of 0.5 kHz. Ultrasound water based coupling gel was used between the device transducer and the skin to obtain effective ultrasound transmission to the fracture.

3. RESULTS

Table 1 presents, data from the time of fracture date, to the start of ultrasound therapy, for each fractured bone. The time from the start of ultrasound therapy to healed fracture, is given in Table 2.

Table 3 shows and overall summary of fracture locations, and Table 4 other procedures combined with ultrasound therapy. In Figures 1 and 2, are shown the result obtained in the radius fracture.

4. DISCUSSION

The specific mechanism, by which ultrasound can stimulated fracture healing, remain unknown. Frequency seems not to be and decisive factor as reported by Duarte [10] and Wang et al. [13]. Nevertheless, the absorption of ultrasound energy depends on the frequency, and this could be an important factor when the ultrasonic beam has to pass trough different type of tissue, taking into account the coefficients of absorption of each one to ultrasound. Moreover, this could be an important factor determining the deep of penetration of the ultrasound in the bone tissue, because of its high absorption coefficient.

The variation of temperature in tissue due to the absorption of energy in the range used by low-intensity pulsed ultrasound (50mW/cm²), is negligible (0.01°C) and insufficient to generate biological responses [10]. However, different paths of action have been reported. Studies in vitro have indicated responses to low-intensity ultrasound, which include, elevated levels of the messages IGF mRNAs, osteocalcin and bone sialoprotein mRNAs [27].

Parvizi et al. [28] reported in the evaluation of the effects of low intensity-pulsed ultrasound on rat chondrocytes in vitro, the increment in level of aggrecan mRNA and in proteoglycan synthesis after three and five treatment of 10 minute a day. Kokubu et al. [29] using an analogous ultrasound signal 20 minutes, examined the regulation of prostaglandin E2 (PGE2) production by ultrasound exposure in mouse osteoblastic cell line, MC3T3-E1. The production of PGE2 in osteoblasts was augmented by ultrasound, which was threefold at 60 min in comparison whit unexposed samples. They evaluated the expression of cyclooxygenase-2 (COX-2) mRNA, which is a critical enzyme for PGE2 production, and found that ultrasound rapidly up-regulated the expression of COX-2 mRNA in a time dependent manner. In addition, PGE2 production by ultrasound was drastically suppressed by a selective inhibitor of COX-2.
Table 1
*Time from fracture date to the start of ultrasound therapy.*

<table>
<thead>
<tr>
<th>Bone</th>
<th>Subtotal</th>
<th>0-90 days</th>
<th>91-150 days</th>
<th>151-270 days</th>
<th>No-unions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scaphoid</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Humerus</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tibia</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Radius</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metacarpal</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2
*Time for the start of ultrasound therapy to healed fractures.*

<table>
<thead>
<tr>
<th>Bone</th>
<th>Subtotal</th>
<th>0-90 days</th>
<th>91-150 days</th>
<th>151-270 days</th>
<th>No-unions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scaphoid</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Humerus</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tibia</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Radius</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metacarpal</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total (no failed)</td>
<td>12</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3
*Overall summary by fracture locations.*

<table>
<thead>
<tr>
<th></th>
<th>Scaphoid</th>
<th>Humerus</th>
<th>Tibia</th>
<th>Radius</th>
<th>Metacarpal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Healed</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Failed</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Table 4
*Others procedures combined with ultrasound therapy.*

<table>
<thead>
<tr>
<th>Bone</th>
<th>Subtotal</th>
<th>Internal fix + pepiculed bone craft</th>
<th>External fixation</th>
<th>External fix + internal fix +</th>
<th>Internal fix</th>
<th>Caster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scaphoid</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Humerus</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tibia</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Radius</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metacarpal</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total Healed (12)</td>
<td>12</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failed (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
They postulated that this results provide a strong
evidence that PGE2 production in osteoblast is
dependent upon the induction of COX-2 mRNA
expression by ultrasound and offer a mechanistic
insight how ultrasound accelerates fracture repairs.
Other studies have reported a modification of calcium
incorporation by low-intensity ultrasound in cartilage
and bone cell \textit{(in vitro)}, and a vinculum between
physical stress and prostaglandin E2 in the remodeling
of bone \cite{30}, \cite{31}

\textbf{Generator technical characteristics.} The generator
has been implemented using a Theramed 1000
ultrasound therapy unit. It is an advanced
microprocessor-controlled apparatus, designed for
continuous and pulsed operations.
Nevertheless, for using the equipment in this
application, it had to be modified for new
requirements. In the electronic circuit, the principal
modification was made to the data acquisition system,
to improve the accuracy of the readings of analogical
signals used to calculate the effective ultrasound
intensity send by the equipment to the medium.
Furthermore, almost all the internal program was
modified, taking into account the changes made to the
communication with the user, the new type of pulsed
mode, and a better accuracy in the calculations of
ultrasound intensities.

\begin{center}
\begin{tabular}{|l|}
\hline
\textbf{Ultrasound transducer} & 25 mm piezoceramic (PZT)  
disc with an aluminum front  
plate of $\lambda/2$ thickness. \\
\hline
\textbf{Frequency} & 1 MHz. \\
\hline
\textbf{Ultrasound intensity} & from 20 to 50 mW/cm$^2$, 
selected in steps of 10 
mW/cm$^2$ (SATA). \\
\hline
\textbf{Treatment time} & Form 1 to 30 minutes 
selected in steps of 1 minute. \\
\hline
\textbf{Application mode} & Pulsed. \\
\hline
\textbf{Pulse burst width} & 400 $\mu$s containing 
approximately 400 sine-
wave pressure pulses. \\
\hline
\textbf{Pulse repetition rates} & 0.5 KHz. \\
\hline
\end{tabular}
\end{center}

*Spatial Average- Temporal Average

\textbf{Equipment operation.} As it was pointed out, the
Theramed 1000 is a microprocessor-controlled unit.
Each time it is switched on, it performs an initialization
routine and a self-check of its principal parameters and
circuits. In addition, it does the necessary adjustments,
according to the transducer that is being employed.
During this process, just a few seconds, all the
indicators light, for a first visual test. Further, if some functioning problem is found in this process, the normal presentation of the equipment is stopped and the error is reported with a specific error code in the unit display.

For an easy understanding of the apparatus operation, a typical selection of a treatment is described. See Figure 2, for a view of Theramed 1000 Front Panel.

After a valid treatment parameter set are selected, if none of the keys is depressed for approximately three seconds, with values of treatment time and ultrasound intensity different from zero, the equipment will recognize the current selection as valid for a treatment. Then, the buzzer sounds, indicating the equipment is waiting for an acoustical contact on the treatment head to start the application. Once this condition has been detected, the ultrasound output power is adjusted to the preset value, and the timer starts the running, which is indicated in the LCD display by two flashing points. Only the time of effective acoustical contact is counted.

There are three LED’s in the treatment head that light in the no-acoustical contact condition. If the lack of acoustical contact is more than 2 seconds, it is seen as permanent, and in addition, it is indicated by a buzzer sound. All events advised by the buzzer, use different sonorous signals. Beginning and end of the treatment are signaled too.

![Fig. 3 - Theramed 1000 Front Panel.](image)

### 5. CONCLUSIONS

The results obtained in the realization of this study, about the use of low-intensity pulsed ultrasound in the treatment of bone fractures, point to confirm the international reports as a valid and useful therapy for this subject, and encourage us to continue employing this technique to clinical application.

### Acknowledgements

The authors acknowledge the contribution in the execution of this study to Lic. A. Ruiz MD, Lic. O. Sánchez and Lic. H. Calás, for setting the methodology and for carry out the ultrasonic calibration of the equipment, to Ing. R. Castillo, Lic. M. Castillo MD and Lic. C. Fernández for the collaborations in the equipment construction and Lic. E. Moreno Ph.D. for his collaboration in the ultrasound transducer implementation.

### REFERENCES


TERAPIA DE ULTRASONIDOS CON PULSOS DE BAJA INTENSIDAD PARA LA REPARACIÓN DE FRACTURA DE HUESOS: ESTUDIO PRELIMINAR

RESUMEN

Se ha mostrado en muchos estudios clínicos que los pulsos ultrasónicos de baja intensidad en el margen empleado en aplicaciones de diagnóstico, pueden ser un medio eficaz para acelerar la reparación de fracturas en huesos. Este trabajo presenta los resultados obtenidos en un estudio efectuado en el hospital “Comandante Manuel Fajardo” en La Habana, Cuba, entre abril del año 1999 y febrero del año 2000. Un total de doce casos, que incluyeron nuevas fracturas, uniones tardías y ninguna unión de los huesos, se trataron periódicamente durante veinte minutos con una señal de pulsos ultrasónicos de 30 mW/cm² (SATA), y ancho “burts” de 400 µs con una frecuencia de 0,5 kHz. Los tratamientos se aplicaron hasta que las fracturas eran clínicamente y radiográficamente sanas. La fijación de metal estaba presente en nueve de ellos. Además, se presenta las características técnicas del equipo diseñado según las normas IEC, el cual está formado por un microprocesador avanzado, para el control y generación del ultrasonido terapéutico.