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Original Article

Effect of low-intensity pulsed ultrasound on regeneration of joint cartilage in patients with second and third degree osteoarthritis of the knee

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ABSTRACT

Objective: To determine if the application of low intensity pulsed ultrasound (LIPUS) therapy has a positive effect over the cartilage repair, functional status, and reduction of pain in patients with grade 2 or 3 osteoarthrosis of the knee.
Design: This trial was an observational, before and after study without a control group, in which 10 patients (11 knees) were studied. We applied LIPUS therapy with an intensity of 0.3 W/cm^2, duty cycle of 50%, giving a total of 36 J/cm^2 per session during 36 sessions (3 months). The clinical measures were obtained before the first session and at the end of the 36th session, and were: cartilage thickness by the analysis of magnetic resonance images (MRI) measured by 2 rheumatologists and a radiology specialist, pain by a visual analog scale (1–10 cm) and function/severity by the Lequesne index. We used the non parametric tests of Wilcoxon for comparing medians and the Spearmans rho for the correlation of the inter observer cartilage thickness measurements defining a P value of <.05 as significant.
Results: We observed an effect on pain (VAS mean before 7.09 [2.54]; mean after 4.18 [2.22]; P=.005) and on the function/severity index (Lequesne mean before 10.55 [5.42]; mean after 5 [4.45]; P=.008). There was poor consistency regarding the cartilage thickness measures by resonance imaging between the 3 observers (2 rheumatologists and 1 radiologist) so we were not able to define the presence or absence of effect on cartilage thickness augmentation.
Conclusions: LIPUS has a benefic effect over pain and functionality/severity in patients with Kellgren and Lawrence grade 2 and 3 osteoarthritis of the knee. Unfortunately in this study we did not count with a reliable measure method to conclude on its effect over cartilage thickness measured by MRI.

Efecto del ultrasonido terapéutico pulsátil de baja intensidad sobre la regeneración del cartílago articular en pacientes con gonartrosis de segundo y tercer grado

Palabras clave:
Ultrasonido terapéutico pulsátil de baja intensidad
Gonartrosis
Reparación de cartílago

RESUMEN

Objetivo: Indagar si la aplicación del ultrasonido terapéutico pulsátil de baja intensidad (USTPBI) produce cambios favorables en la regeneración del cartílago articular, así como beneficios clínicos en pacientes que tienen gonartrosis grado 2 o 3 según la clasificación de Kellgren y Lawrence.
Diseño: Éste es un estudio observacional, tipo antes y después, sin grupo control, en el que se estudiaron 10 pacientes (11 rodillas) con gonartrosis grados 2 y 3 (según la clasificación de Kellgren y Lawrence), a los que se les aplicó ultrasonido terapéutico a una intensidad de 0,3 W/cm^2 pulsátil al 50%, que otorgó un total de energía de 36 J/cm^2 por sesión durante 36 sesiones. Las mediciones se realizaron previas al inicio del tratamiento y posteriores al término de éste (3 meses después), y consistieron en: grosor del cartílago articular mediante el análisis de imágenes tomadas por resonancia magnética (RM) por 2 reumatólogos y un experto radiólogo; dolor mediante escala visual analógica (de 1 a 10 cm) y el índice de gravedad de Lequesne.

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Se utilizaron pruebas estadísticas no paramétricas de Wilcoxon y pruebas de correlación de Spearman, y se definió un valor de p < 0,05 como estadísticamente significativo.

Resultados: Se observó una disminución en la intensidad de dolor (basal media de 7,09 ± 2,54; final media de 4,18 ± 2,22; p = 0,005) y una mejoría en cuanto a la funcionalidad (basal media de 10,55 ± 5,42; final media de 574,45; p = 0,008) después del tratamiento con USTPBI. Con respecto al grosor medido en la RM, no se obtuvieron mediciones consistentes entre los observadores, por lo que se concluyó que el método de medición no fue reproducible, lo que hizo difícil definir si hubo un incremento o no en el grosor del cartílago articular.

Conclusiones: El USTPBI tiene un efecto benéfico sobre la disminución del dolor y la mejoría de la funcionalidad. Desafortunadamente, en este estudio no se cuenta con un método de medición reproducible para arrojar una conclusión válida en cuanto al efecto del USTPBI sobre el grosor del cartílago articular

Joint degenerative disease (JDD) is a chronic and degenerative affection of all of the joint structures, which starts as damage to the cartilage and progresses though a dynamic adaptation response, leading to irreversible structural change.[1]

According to the data from the Framingham study, knee osteoarthritis occurs in at least 33% of persons 60 or older[1] and is the main cause of joint inflammation in the United States, with a prevalence of 12%.[2–4]

With respect to non-pharmacologic treatment, therapeutic ultrasound (TUS) is an important tool, which favors cartilage regeneration.[5]

TUS is based on the emission of mechanical waves of frequencies over 16 000 Hz, which interact with the bodily tissues and lead to vibrations of an elevated frequency, resulting in either a thermal or a mechanical effect.[5] In order to achieve the mechanical effect, the sound wave must be applied as a pulse and at a low intensity.

In the medical literature there is ample evidence for the mechanical effect of low-intensity and pulse ultrasound which favors cell metabolism and the capacity of tissue regeneration.[6–9]

Studies in humans have shown a beneficial effect on bone healing in fractures when using this treatment modality,[6,7] making the application of pulse therapeutic ultrasound (PTUS) useful in tissues such as joint cartilage by producing a regenerative effect.

On the other hand it is important to mention that TUS in general is better diffused in liquid environments (with a high water content), such as in the case of the knee.[10]

Several studies have shown a positive effect of PTUS on the proliferation of stromal cells and chondrocytes, as well as in the differentiation of mesenchymal stem cells[11–13]; there is also an effect on metabolic stimulation and the formation of extracellular matrix in chondral tissues and an improvement in the histological appearance of total osteochondral damage in animals.[13–15]

Cook et al demonstrated a positive effect of treatment with PTUS on joint cartilage in the repair of osteochondral defects induced in the knees of rabbits: they applied a dose of 36 to 72 J/cm^2 daily for 3 months and reported both macroscopic and histological benefits.[14]

Until today there are no studies on the effect of PTUS on joint cartilage in patients with knee osteoarthritis. Therefore, the objective of this study is to investigate the effect of this treatment modality on the thickness of the joint cartilage, pain and function of patients with knee osteoarthritis stage 2 and 3 according to the classification of Kellgren and Lawrence.[16]

Material and methods

Design

Observational, before and after study, without a control group.

Subjects

The study group was composed on 10 patients who belonged to the Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE) health system: nine women and 1 man, mean age 67.18 years with an age range of 56 to 81 years of age, with a diagnosis of knee osteoarthritis (according to the criteria of the American College of Rheumatology)[17] stages 2 and 3 (according to the classification by Kellgren and Lawrence)[16], recruited in the period between March 1, 2007 and May 30, 2007, sent by the departments of Rheumatology, Geriatrics, Orthopedics and Physical Rehabilitation of the Centro Médico Nacional (CMN) 20 de Noviembre.

The exclusion criteria were to be carriers of an inflammatory rheumatic disease, having undergone a knee infiltration in the 12 weeks prior to the study and to have any formal contraindication for the performance of a Magnetic Resonance (MR) imaging study.

This study was approved by the Ethics committee of the CMN 20 de Noviembre.

Measurements

Pain

Measured using a 10 cm visual analog scale (VAS) (EVA) on 2 occasions: 10 cm on 2 occasions: one day before the start of treatment and one after the application of session number 36 of PTUS.

Function

A severity index of Lequesne[18] was employed one day before the start of treatment and one day after session 36 of PTUS. A reduction in 3 points was considered as important clinical improvement, in accordance to what has been reported in the literature.[19]

Thickness of joint cartilage

Two images were performed (pretreatment and post-treatment) using MR with an Intera set of 1.5 Tesla, 3D/WATSc sequence in a coronal projection, T1 FFE TR 20 TE 10 and Flip 25 technique, obtaining 30 coronal slices of 3 mm thickness on the examined knee. Position of the knees was taken into account (flexion and rotation angles) with the objective of obtaining post-treatment images comparable to the initial ones (using real-time comparisons).

Once the images had been obtained, they were printed on photographic paper but not labeled and taken to 2 independent observers of the Hospital General de México (J.C. and C.H.C), who did not know the origin, pretreatment or post-treatment stages of the images, and to an expert in the interpretation of MR in soft-tissues (Judith Vázquez Zamudio) at the CMN 20 de Noviembre.

These observers performed the measurement of joint cartilage thickness in randomly assigned but symmetrical areas in the images corresponding to the same patient and on paper using scale measuring

(1:20 scale). Regarding the observations of the rheumatologists (J.C. and C.H.C.), they were submitted for agreement testing with a result under 35%, which led to the decision to perform a new joint measurement; final measurements were reached by consensus. In the case of measurements performed by an expert, they were carried out in a single session.

The rheumatologist's measurements and those of the expert were then submitted to a correlation statistical analysis.

Therapeutic intervention

A Intellect Mobile model Chatanooga therapeutic ultrasound apparatus was employed, with the following parameters: pulse mode at 50%, intensity 0.3 W/cm^2 and frequency of 1 MHz, with an energy output of 36 J/cm^2 based on the dose used by Cook in a study with rabbits.[14]

To calculate the time of application we used the measurement of the tibial plateau area obtained in the initial MR, multiplied it by a factor of 2 to obtain an approximate value of the total area to be treated and in order to obtain the time needed to deposit the abovementioned energy using the following formula:

$$\frac{\text{Time (s):energy (36 J/cm}^2)\times\text{area to treat (cm}^2)}{\text{Potency (0.3 W/cm}^2\times 7\text{ cm}\times 0.5)}$$

Application of PTUS was performed by physical therapy specialists in the department of Physical Rehabilitation of the CMN (8 in total) and was performed as follows (Figure):

– 30° flexed knee (using a cloth in the popliteal area)
– PTUS application approach in 2 times (medial and lateral compartments)
– Semifixed head coupling technique (horseshoe)

The duration of treatment was 3 months with a frequency of 3 sessions a week and a total of 36 sessions; the total cost of these was 7200 Mexican pesos (200 pesos per session).

Figure. Application technique of low-intensity pulse therapeutic ultrasound.

A possible secondary effect of TUS application, due to a phenomenon known as cavitation, consist in the creation of a vacuum between the tissues that lead to inflammation and is manifested as pain and edema.

Statistical analysis

Wilcoxon's test for related variables was employed in order to compare the earlier variables of pain, severity and thickness in millimeters with the later ones. In addition, Spearman's correlation test was employed for observations performed by rheumatologists (J.C.) and the expert radiologist (J.V.Z.). For this we employed the SPSS version 12 statistical software.

Results

A group of 10 patients (11 knees) was studied, formed by 9 women and 1 man, with a mean age of 68 years (standard deviation [SD], 8.7), a mean weight 72 kg (SD, 9.86), a mean height of 153 cm (SD, 6.14) and a body mass index of 30 (SD, 5.8).

Within the study group there was a severity (according to the classification of Kellgren and Lawrence)[16] of stage 2 in 5 patients (50%) and stage 3 in 5 patients (50%).

With respect to the thickness of the cartilage, measured in millimeters, Spearman correlation test showed an absence of this with the exception of the cartilage measured in the medial femoral compartment in the initial image (r=0.73; P=.011) (Table 1).

No significant differences were seen between the baseline and post-treatment cartilage thickness measurements, with the exception of the lateral tibial compartment where a decrease of this was seen in the observations performed by the rheumatologists. (P=.028) (Table 2).

Joint pain (measured by VAS) showed a significant reduction (initial mean, 7.,09; final mean, 4.18) with a significant P of .005.

The Lequesne degree of severity showed a significant reduction (initial mean, 10.55; final mean, 5) with a significant P of .008, interpreted as clinical improvement[19] (Table 2).

Discussion

Knee osteoarthritis has an important impact on the quality of life and functionality of patients that present it, and there is a tendency towards an increase in prevalence of this disease explained by the increase in life expectancy of the general population.

To date there are no effective therapeutic interventions proven to halt the progression or invert the loss of joint cartilage in patients with knee osteoarthritis. Therefore, pain secondary to this affection will continue to impact the quality of life of patients presenting it.

The MR technique described in this study is within the recommendations suggested by OMERACT (Outcome Measures in Rheumatology Clinical Trials) and OARSI (Osteoarthritis Research Society International) used to define the most useful and reproducible techniques for the measurement of joint cartilage in the knees.[20]

Without a doubt, one of the main problems for the evaluation of the different treatments of knee osteoarthritis is how to measure the amount of joint cartilage. Within the available diagnostic tools, MR

Table 1
Correlation between cartilage thickness measurements performed by rheumatologist in consensus and the measurements performed by the expert

	MBFT	MCFT	LBFT	LCFT	MBTT	MCTT	LBTT	LCTT
Spearman Rho	0.731	0.229	0.248	0.243	0.407	−0.170	−0.086	0.012
P	.011	.498	.462	.472	.214	.617	.802	.973

LBFT indicates lateral baseline femoral thickness; LBTT, lateral baseline tibial thickness; LCFT, lateral control femoral thickness; LCTT, lateral control tibial thickness; MBFT, medial baseline femoral thickness; MBTT, medial baseline tibial thickness; MCFT, medial control femoral thickness; MCTT, medial control tibial thickness.

Table 2
Wilcoxon's test results

	Initial mean (SD)	Final mean (SD)	*P*
Functionality (Lequesne)	10.55 (5.42)	5 (4.45)	.008
Pain (VAS, cm)	7.09 (2.54)	4.18 (2.22)	.005
Consensus measurements on the part of the rheumatologists			
Femoral medial thickness	1,51 (0.58)	1.49 (0.52)	.719
Lateral femoral thickness	1.93 (0.74)	1.76 (0.71)	.168
Medial tibial thickness	1.27 (0.52)	1.33 (0.53)	.493
Lateral tibial thickness	2.06 (0.51)	1.92 (0.58)	.028
Measurements performed by the expert radiologist			
Medial femoral thickness	1.36 (0.54)	1.20 (0.55)	.307
Lateral femoral thickness	0.89 (0.38)	1.09 (0.26)	.085
Medial tibial thickness	1.25 (0.42)	1.16 (0.38)	.507
Lateral tibial thickness	1.10 (0.37)	1.21 (0.45)	.754

Leq indicates Lequesne severity index; VAS, visual analog scale (1-10).

offers the advantage of a complete visualization of the joint cartilage; however, there are many techniques and types of sequences used to obtain the image and the ideal technique for this disease is yet to be established.[20]

During the past years it has been demonstrated that the measurement of the knee joint cartilage volume provides useful data for the evaluation of disease progression and offers an objective measure to determine treatment effect of interventions that attempt to modify the disease,[21] with the disadvantage of requiring semiautomatic software which is not available in all of the imaging centers, such as the primary care unit where this study was performed.

The measurement method used in this study shows a delicate internal validity evidenced by very low correlation values. This definitely reduces the trustworthiness of the measurements performed and shows the existing difficulty in obtaining cartilage measurements that are useful and reproducible.

With respect to the PTUS application technique, the approach zone chosen is within the area defined as ideal for the application of ultrasonic energy to the joint space, according to a study recently performed in cadaver knees and published by White[22]; however, in this study a flexion of 90° was used, while in the present study a flexion of 30° was employed, which might have influenced the correct penetration of the energy in the area of intended treatment.

In the past few years there have been a series of biomechanical studies which indicate that the mechanical stimulus of a joint is essential for its optimal function and maintainance,[23] and positive changes in the chondrocyte metabolism was seen with cyclic charges.[24] As has been previously mentioned, the application of PTUS provides mechanical energy, and therefore is proposed to be a cell regenerator in the cartilage.

Although the results in the joint cartilage are not valid, clinical results are of note; it is undeniable that there is a significant effect with regard to the reduction in pain with a direct implication in functional improvement.

This is related to what has been mentioned in the literature regarding the lack of a direct relationship between pain and the amount of joint cartilage.[21] With respect to function, it must be mentioned that an important part of the improvement detected was due to a reduction in stiffness, as registered by the Lequesne index, debilitating the relationship between pain and function, and finding other factors in which treatment with PTUS seemed to exert influence.

The beneficial effect recorded on pain and functionality could be due to an anti-inflammatory effect on the extra-articular tissue of the knee, to a direct effect on the architecture of the joint cartilage (which could not be shown by the measurements employed) or to a placebo effect. It is important to mention that no adverse events were recorded during or after the application of PTUS in this study.

Without a doubt, the 2 greatest methodological weaknesses of this study are the small sample size and the fact that it lacked a control group (with placebo).

With respect to the cost-benefit relationship, although cost seems to be an issue during the early stages, the impact that the intervention might have on non-steroidal anti-inflammatory drug use (reducing their consumption and therefore their potential adverse events) make this therapeutic tool an important adjuvant for the treatment of symptoms which will reduce the cost of integral treatment in patients with knee osteoarthritis in the long term.

The results shown by this study make it evident that it is important to develop new studies with better experimental designs targeted to responding the question of whether the effect of PTUS on joint cartilage regeneration in patients with knee osteoarthritis is real; new studies that take into account the fact that the regenerative effects on cartilage have been proven in their basic form[11–14] on one hand and the clinical effects on pain and function shown in this study on the other.

It is also important to have diagnostic tools that have high validity and reproducibility with the objective of testing the effect of the therapeutic measurements which pretend to be established as disease modifiers.

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