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The Effect of Metaphyseal Shock Wave Application on the Longitudinal Growth of Femur: A Rat Model

Metafizyal Şok Dalga Uygulamasının Femurun Longitudinal Büyümesi Üzerindeki Etkisi: Rat Modeli

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Abstract: There is an idea that extracorporeal shock wave therapy (ESWT) induces increased blood flow and stimulates the physiological process of bone growth on physis. Also, recent studies have shown that ESWT promotes growth plate chondrogenesis and longitudinal bone growth in rabbits. The aim of the study was to investigate the longitudinal growth of femur bone on a rat model after ESWT application on distal metaphyseal region. The present study used the Multimed 2001- ELMED lithotripter designed for urinary stone treatment on thirty immature rats with unclosed physes. Rats were divided into 3 groups consisting of 10 rats in each group. The age of the rats was ranged from 4 to 6 weeks. To the first group, single dose 0.3 mJ/mm^2, 1000 shock wave; to the second group single dose 0.7 mJ/mm^2, 1000 shock wave; and to the third group 3 doses (1 session weekly period) 0.3mJ/mm^2, 1000 shock wave were applied on the right distal femur metaphyseal region under ketamine anesthesia. The left femurs of the same animals were accepted as controls. Radiological measurements were made digitally with the NetCAD 4.0 engineering program. Metaphyseal shock wave application did not affect the longitudinal bone growth in the early stage ($p>0.05$ in all 3 groups). These results indicate that ESWT applied to the distal metaphysis of the femur had no effect on early longitudinal bone growth based on radiological measurements in rats. Still there is need to further histologic and radiologic studies in this area

Keywords: Animal experimentation, bone lengthening, extracorporeal shockwave therapy, osteogenesis.

Özet: Ekstrakorporeal şok dalga tedavisinin (ESWT) artan kan akışını indüklediği ve fizyolojik kemik büyüme sürecini uyardığı düşüncesi oluşmuştur. Ayrıca, son çalışmalar ESWT'nin büyüme plağında kondrogenezi ve tavşanlarda longitudinal kemik büyümesini arttırdığını göstermiştir. Bu çalışmanın amacı, rat modelinde distal metafizyal bölgeye ESWT uygulaması sonrası femur kemiğinin longitudinal büyümesini araştırmaktır. Bu çalışmada, fizisleri kapanmamış otuz immatür rat için üriner taş tedavisi için tasarlanmış Multimed 2001- ELMED litotriptör cihazı kullanıldı. Ratlar her grupta 10'ar denek olmak üzere 3 gruba ayrıldı. Ratların yaşı 4 ile 6 hafta arasında değişmekteydi. Birinci gruba tek doz 0.3 mJ/mm2, 1000 şok dalgası; ikinci gruba tek doz 0.7 mJ/mm2, 1000 şok dalgası; üçüncü gruba ise 3 doz (haftalık periyotlarla 1 seans) 0.3 mJ/mm2, 1000 şok dalgası ketamin anestezisi altında sağ distal femur metafizyal bölgesine uygulandı. Ratların sol femurları kontrol olarak kabul edildi. Radyolojik ölçümler NetCAD 4.0 mühendislik programı ile dijital olarak yapıldı. Metafizyal şok dalgası uygulaması erken dönemde longitudinal kemik büyümesini etkilemedi (3 grupta da $p>0.05$). Bu sonuçlar, femurun distal metafizine uygulanan ESWT'nin ratlarda radyolojik ölçümlere dayalı olarak erken dönemde longitudinal kemik büyümesi üzerinde etkisi olmadığını göstermektedir. Yine de bu alanda daha ileri histolojik ve radyolojik çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Hayvan deneyleri, Kemik uzaması, Ekstrakorporeal şok dalga tedavisi, sıçanlar.

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1. Introduction

Recently, the studies have been directed to the treatment of the disorders of bone and soft tissue by extracorporeal shock wave therapy (ESWT) which was mainly developed for the treatment of urinary stones [1,2].

The initial studies were concentrated on fracture and bone healing. The findings that shock waves produced microfractures on the bone which induced callus formation, directed the investigators to study the effects on delayed unions and pseudoarthrosis [3,4].

Currently, some physicians dealing with skeletal system have expanded the use of ESWT to include the treatment of calcifying tendinitis, pseudoarthrosis, chronic low back pain, tendinitis, lateral epicondylitis, calcaneal spur, and shoulder impingement diseases. However, the effect of shock waves on bone tissue remains controversial [4-12].

Studies on the skeletal system revealed that shock waves increased osteogenic potential, induced subperiosteal petechial hemorrhage on the cortical bones with consequent thickness of the periosteum due to fibrosis of petechial areas. Additionally, it has been theorized that mechanotransduction seems to be underlying mechanism which allows ESWT to spread out energy into cells, stimulate the bone lacunae-canalicular system and convert the physical stimulus into biochemical signals [3-8,13-15].

Since our literature survey failed to find any data concerning the study with the effect of ESWT on metaphysis, the present study aimed to investigate the longitudinal growth of femur bone on a rat model by the light of the idea that ESWT will induce blood flow and the physiological process of bone growth on physis.

2.Materials and Methods

2.1.Shock waves

The present study used the Multimed 2001 (ELMED, Turkey) lithotripter designed for urinary stone treatment, and focusing was achieved by C-armed X-ray fluoroscopy. The focal distance of this equipment was 1235 mm with 1200 bar mean focal pressure. From 0.1-0.7 mJ/mm^2 shock waves with a frequency of 70/min were generated in a 3.7 litre water pad by electrohydrolic spark gap shock wave generator. The treatment table was specially designed to move on three planes enabling focus on the treatment area.

2.2. Animals

The animals were treated in accordance with the guidelines of the Yüzüncü Yil University Animal Experiments Local Ethics Committee (Decision No:185125/21). Twenty nine cross-breed rats were kept in specially designed cages that fit the criteria of Canadian Council on Animal Care. The area was lighted in the day time and kept dark at night so as not to disturb their biorhythmicity. Their ages ranged between 4 weeks and 6 weeks. They weighed between 60-90g, and their long bones were immature with open physes.

2.3. Method

Posterior right legs of the rats were shaved for a better contact to the lithotripter pad. The animals were anesthetized with 1.5 ml/kg intramuscular (IM) ketamine hydrochloride 3 minutes prior to the procedure. The rats were randomly allocated into 3 groups consisting of 10 rats in each group. The age of the rats was ranged from 4 to 6 weeks. The shock wave magnitude was determined with an energy level of 0.3-0.7 mJ/mm^2 [16,17]. To the first group, single dose 0.3 mJ/mm^2, 1000 shock wave; to the second group single dose 0.7 mJ/mm^2, 1000 shock wave; and to the third group 3 doses (1 session weekly period) 0.3 mJ/mm^2, 1000 shock wave were applied on the right distal metaphyseal region, after confirming the physeal openings under fluoroscopy (Fig 1.).

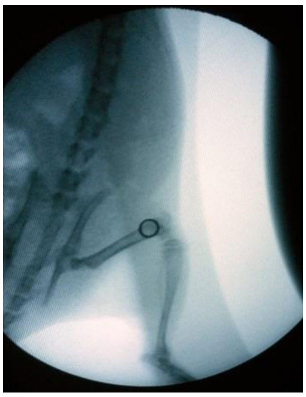

Figure 1. Confirmation of the physeal openings under fluoroscopy

The focusing was repeatedly checked by fluoroscopy to reduce minimal deviations. The left femurs of the same animals were accepted as controls. The rats were left to act freely for 48 hours after the procedure to observe local dermal changes on the treatment area of limbs. They were then returned to their cages following the 3rd day for four weeks observation. Four weeks after the applications, the subjects were sacrificed by cervical dislocation. Only radiological measurements made on the femur bones were examined, as histological preparations taken from the metaphysis area due to the accident damaged.

The distance from the tip of trochanter major (the most proximal point of trochanter major, point A) to the most distal point of lateral condyle (point B) was recorded as femoral length in each group (Figure 2.).

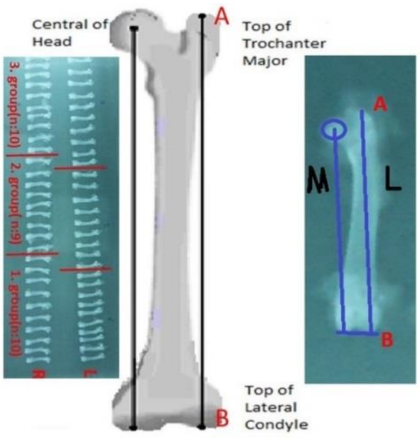

Figure 2. Measurements of femoral length are only shown for explanation. **A**, the most proximal point of trochanter major. **B,** the most distal point of lateral condyle. (↕),

Radiological measurements were made digitally with the NetCAD 4.0 engineering program. The difference between lengths of the control and treated femur was regarded as representing *induced growth*. To ensure interobserver reliability, the measurement was made by two different individuals in different times, and kappa statistic was used. Kappa values higher than 0.75 may be regarded as excellent interobserver agreement, and those below 0.40 as poor agreement [18]. Student's t-test and Mann Whitney-U tests were used for statistical analyses.

3.Results

There was a close agreement among the investigators, and interobserver reliability showed an excellent agreement (kappa = 0.80).

The findings of each group were as follows:

Group 1 (**single dose 0.3 mJ/mm^2, 1000 shock waves**)

Clinical observation did not show any limp or petechial haemorrhage in the treatment area. Radiographic examination revealed no statistical difference between treated and untreated femur lengths (p=0.199; 0.708) (Table 1).

Table 1. Medial and Lateral measurement comparisons of ESWT-applied and non-applied femur lengths of Group 1

	N	**Mean Femur length (mm) ± Std. Deviation**	**Mean Difference of Femur lengths (mm)**	***p***
ESWT-applied-femur (Group 1) Lateral measurements	10	30.441 ± 0.35	0.194	0.199
ESWT-non-applied-femur (Group 1) Lateral measurements	10	30.246 ± 0.299		
ESWT-applied-femur (Group 1) Medial measurements	10	29.722 ± 0.361	0.055	0.708
ESWT-non-applied-femur (Group 1) Medial measurements	10	29.667 ± 0.285		

Group 2 (single dose 0.7mJ/mm^2, 1000 shock waves)

Dermal petechial haemorrhaging was seen in two rats. Limping of the affected legs was observed in the other two rats which continued for 48 hours. Radiographic examination revealed no statistically difference between treated and untreated femurs lengths (*p*=0.741; 0.943) (Table 2).

Table 2. Medial and Lateral measurement comparisons of ESWT-applied and non-applied femur lengths of Group 2

	N	Mean Femur length (mm) ± Std. Deviation	Mean Difference of Femur lengths (mm)	*p*
ESWT-applied-femur (Group 2) Lateral measurements	9	30.432 ± 1.231	0.196	0.741
ESWT-non-applied-femur (Group 2) Lateral measurements	9	30.236 ± 1.243		
ESWT-applied-femur (Group 2) Medial measurements	9	29.551 ± 1.116	0.055	0.943
ESWT-non-applied-femur (Group 2) Medial measurements	9	29.592 ± 1.268		

Group 3 (3 doses 0.3 mJ/mm^2, 1000 shock waves)

Dermal petechial haemorrhage and limping were absent. Radiographic examination revealed no statistically difference between treated and untreated femurs lengths (*p*=0.946; 0.911) (Table 3).

Table.3. Medial and Lateral measurement comparisons of ESWT-applied and non-applied femur lengths of Group 3

	N	Mean Femur length (mm) ± Std. Deviation	Mean Difference of Femur lengths (mm)	*p*
ESWT-applied-femur (Group 3) Lateral measurements	10	29.9730 ± 1.058	0.028	0.946
ESWT-non-applied-femur (Group 3) Lateral measurements	10	29.9445 ± 0.761		
ESWT-applied-femur (Group 3) Medial measurements	10	29.2245 ± 1.010	-0.047	0.911
ESWT-non-applied-femur (Group 3) Medial measurements	10	29.2715 ± 0.834		

4. Discussion

ESW has been used since the 1980s to treat urinary stones, and its effects on tissue and organ systems have been systematically investigated during the last 20 years [1,13,14]. In vivo and in vitro studies on the effects of shock waves on bone and related tissues also started in the early 1980s. Successful results in the treatment of pseudoarthrosis, an important problem for orthopaedic surgeons, have been reported since then [14,19]. Although studies have been conducted on the effects of shock waves on the bone cortex, periosteum, diaphysis, and epiphysis, there are few studies on such effects on the metaphysis and longitudinal bone growth has been reported in literature.

The distal femur metaphysis was selected for the treatment area because this area is known to supply 70% of femoral growth and 40% of the overall growth of the lower extremity [20]. Another important reason for choosing the distal femur metaphysis in our study is that the metaphysis is well-vascularized, and the wide bone surface facilitates significant bone formation [21]. Due to these properties, we aimed to determine the angiogenetic and osteogenetic effects of ESW.

Other studies indicated that the optimum shock wave magnitude was between 1000–2000 with an energy level of 0.3-0.7 mJ/mm² [16,17]. Energy levels up to 1.0-1.5 mJ/mm² resulted in bone fractures and necrosis [17,22]. For this reason, 1000 shock waves at 0.3-0.7 mJ/mm² were used in the current study

A Multimed 2001 lithotripter, designed for treating urinary stones, was used in the current study. This equipment is mainly composed of an electrohydraulic shock wave generator and an ellipsoid acoustic mirror for focusing. Orthopaedic ESW therapy equipment usually incorporates an electromagnetic shock wave generator and an acoustic lens. The orthopaedic equipment is more accurate in focusing, which is particularly important due to the small dimensions of the rat metaphysis. We encountered difficulties in maintaining the focus on the metaphysis because of the wide focal area of the electrohydraulic shock wave generator. The nature of the tissue at the treatment site also appears to be an important factor. In a review, it was noted that ESW increases osteoblastic activity and aids bone healing by enhancing the release of cytokines and growth factors such as BMP, TGF-ß, CBF-a1, VEGF, IGF, FGF, and PDGF [23]. Catalano et al. demonstrated that ESW accelerates bone formation by inducing the transformation of adipose-derived stem cells into osteoblast-like cells [24]. In an animal study conducted on rabbits, high-energy radial shock wave treatment was applied to the proximal tibia, and longitudinal bone growth was shown to increase [25]. Conversely, Guisti et al. applied shock waves to the proximal tibia in rabbits but found no difference in longitudinal bone growth or histopathology compared to the control group [26]. Similarly, Graff et al. reported the ineffectiveness of shock waves delivered to diaphyses on longitudinal bone growth [13]. Notably, in our study, metaphyseal shock wave application did not affect longitudinal bone growth in the early post-treatment stage (45 days after treatment).

The angiogenic and osteogenic effects of ESWT on bone contribute to bone healing by increasing cortical bone formation [27]. An animal study demonstrated that unfocused ESWT increased cortical and trabecular bone volume, suggesting that temporary damage to the bone marrow might be the reason for this anabolic effect [28]. Additionally, ESW enhances anabolic cytokines such as BMP2, increasing bone strength and recovery [29]. In a clinical study examining the effect of ESWT on bone mineral density in 64 postmenopausal osteoporotic patients, high-dose ESWT was shown to increase local bone mineral density [30]. One of the main limitations of our study is that we did not evaluate the effects of ESWT on bone mineral density and its histopathological effects on bone. Further histopathological studies on this subject are needed.

Our hypothesis in this study was that metaphyseal shockwave therapy could have either positive or negative effects on bone osteogenesis, which may influence its potential use in clinical treatment. As a result, shock waves focused on metaphysis did not increase the longitudinal growth of immature rat femurs in our study. Due to the proximity of metaphysis to epiphysis, minimal deviations in focusing the waves negatively affect the epiphysis, potentially decreasing or arresting normal growth. Despite our negative results, further studies comparing the effects of shock waves applied to metaphysis and diaphysis are required to establish the clinical safety and effectiveness of this promising modality.

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