International Society for Musculoskeletal Shockwave Therapy - ISMST

ISMST

Newsletter

VOLUME 1, ISSUE 1

Editorial Office
Avenida Pacaembu,1024
CEP 01234-000 - São Paulo - Brazil
Fone: 55-11-3825·8699
E mail : prds@uol.com.br

website: www.ismst.com

Inside this Issue

Editor's Note 1
President's Message 1
8th International Congress of the ISMST 2
Biological Mechanism of Musculoskeletal Shockwaves 5
Effects of Extracorporeal Shockwave Treatment on equine tendon healing 12
Instructions for Authors 15

MC 540/05 03-2006-ACX-05-BR-540-PB

Editorial · Editor's Note

Taking on the challenge of publishing an International Magazine of Shockwave Therapy is justified by the great progress in clinical research and results that have been made known in several scientific publications and in international conferences. Many researchers have dedicated themselves to the development of this technology all around the world. The International Society for Musculoskeletal Shockwave Therapy, founded in 1997 and headquartered in Wien, was an important landmark and was made possible thanks to the extraordinary efforts of researchers Dr. Wolfgang Schaden and Richard Thiele. Many others could be mentioned but I'd like to remember Dr. Chen Jin Wang, whose work can help us find answers to many important questions and whose research will play an essential role in this publication.

This publication is open to doctors, veterinarians and physicists who wish to publish their findings in this field. Initially, our projection is for three annual editions.

On behalf of the ISMST, we thank Merck Sharp & Dohme do Brazil for their support which made this publication possible. Finally, we hope to contribute effectively to the development and to increasing awareness about the Extracorporal Shockwave Therapy.

Paulo Roberto Dias dos Santos

O desafio de iniciarmos a publicação de uma Revista Internacional de Ondas de Choque é plenamente justificada pelo grande avanço nas pesquisas e nos resultados clínicos alcançados, divulgados em várias publicações científicas e em Congressos Internacionais. Vários pesquisadores têm nos últimos anos se dedicado de forma expressiva ao desenvolvimento desta tecnologia no mundo. A *International Society for Musculoskeletal Shockwave Therapy*- ISMST fundada em 1997 com sede em Viena - Áustria foi um marco importante na consolidação desta, graças ao trabalho incansável dos pesquisadores Dr. Wolfgang Schaden e Richard Thiele, que são responsáveis por boa parte do sucesso alcançado. Muitos outros poderiam ser citados ,cada um com sua importância, mas um em especial deve ser lembrado o Dr. Chen Jin Wang que tem respondido através de seus trabalhos muitas questões importantes e certamente terá papel fundamental nesta publicação.

Esta publicação é aberta a médicos, veterinários, físicos e pesquisadores que queiram divulgar seus trabalhos nesta área. Inicialmente estão previstas três edições anuais.

Em nome da ISMST agradecemos o apoio dado pela empresa Merck Sharp & Dohme do Brasil sem a qual não seria possível a realização desta.

Finalmente, esperamos contribuir de forma efetiva para o desenvolvimento e divulgação da Terapia por Ondas de Choque Extracorpórea.

President's Message

It is a great pleasure for me to welcome you all as members of our Society at the first Newsletter of ISMST in 2005.

Since 1997 when ISMST was founded in Vienna, the development of extracorporeal shock wave therapy has grown with recent scientific findings and clinical studies in spite of the initial scepticism in the orthopedics surgeons community. A small group of pioneers has become a renowned international society with more than 492 members of 53 countries and, in the last Annual General Meeting of the ISMST on May 30th 2005, 81 new members from 32 countries were accepted.

In all ISMST's meetings that I have been participated, we have discussed about more possibilities to divulgate the Shock Wave Therapy in our countries to find a general medical interest and to keep the minds open to discuss about the understanding, the efficacy and security of this method.

I really think that a Newsletter is a good idea and an excellent way to share scientific knowledge and the latest news about extracorporeal shock wave therapy.

I hope you will be active participants therefore you will cultivate the spirit of international exchange of ideas, a very healthy habit of this "shockwave family".

Congratulations!

I am looking forward to seeing you all in Rio de Janeiro for the ISMST Congress in 2006.

Ana Claudia Souza *- ISMST President*

8th International Congress of the ISMST International Society for Musculoskeletal Shockwave Therapy May 29th - June 1st, 2005

Vinzenz Auersperg[1], Wolfgang Schaden

The International Society for Musculoskeletal Shockwave Therapy (ISMST) has been founded 1997 in Vienna, the development has been fast and the society now has about 500 members from 53 countries from all over the world. The 8th annual congress this year with 250 participants was held at the Vienna Marriott Hotel, 85 papers have been presented form 20 different countries.

The scientific level of the presentations has been high and showed the efficacy of ESWT (extracorporeal shock wave therapy) of the well introduced indications as there are the plantar heel pain, the tennis elbow, the calcifying tendonitis of the rotator cuff and delayed bone healing or pseudarthrosis. Like in Taiwan last year there have been most interesting publications about basic research. Additional we had presentations about study design and about the different special features at the different countries concerning reimbursement and logistical peculiarities.

The highlights of the congress:

During the last years we had a lot of controversial discussions about high level studies with randomized, blinded and controlled design showing contradictory results. Some of the presented studies at that congress helped us to understand the reasons for these contradictions. On the one hand we got clarity into the discussions because of the findings of the basic research; on the other hand we got results of new studies showing possible bias of the conflicting statements. For example there are several studies showing, that local anaesthesia has a negative influence on the outcome of especially low energy shock wave therapy (Jan-Dirk Rompe, Germany; Gerold Labek, Austria).

The results of basic research of the last years changed our thinking about the effects on the treated tissue, they all show changes of the molecular biological structures and enzymatic effects. Shock waves with an energy level used in medicine seldom cause mechanical breakages or ruptures of the tissue. Astonishing is an observation of Wolfgang Schaden at his retrospective investigations of the results of the shock wave treatments of delayed bone healing and pseudarthrosis at the Meidlinger Unfall Krankenhaus in Vienna, he found at several indications better results using less energy and/or less impulses (his over all success rate is about 80% healing after ESWT).

These clinical findings are confirmed by a lot of publications: Markus Maier (Germany) showed in his trials with rats, that osteoneogenesis is possible without mechanical destructions of the tissue and bone respectively. The working groups around Ching-Jen Wang (Taiwan), Sergio Russo (Italy), Helmut Neuland (Germany) and Ludger Gerdesmeyer (Germany) showed impressively the increase of enzymes in the treated tissue, for example VEGF (vessel endothelial growth factor), BMP (bone morphogenetic protein), OP (osteogenetic protein), NO (Nitride oxide) und other enzymes have been proven. There are reasonable doubts on the mechanical hypothesis of shock wave mechanisms, as we discussed 15 years ago, thinking that micro lesions (like ruptures and breakages of the bone or the soft tissue in the focus) caused by ESWT induce healing. The main message of the congress was the understanding, that ESWT does not cause mechanical effects, it causes a microbiological effect, we could say, it causes healing by bioengineering.

A very interesting effect has been found by Ludger Gerdesmeyer (Germany), he demonstrated the antibacterial effect of shock waves, especially at bacteria like Staphylococcus aureus, MRSA.

There has been taken note of new reports about clinical studies according healing after shock wave therapy on osteochondral lesions, particularly the papers of Helmut Neuland (Germany), Hideshige Moryia (Chiba/Japan) and Richard Thiele (Berlin) have been discussed extensively due to the impressive success of that treatment.

An international press conference held on May 31st, 2005 at the conference venue had good response. Otto Hess (cardiologic professor at the Inselspital Bern, Switzerland) presented the results of his investigations regarding revascularisation of ischemic myocardium thru shock wave therapy, Hildegunde Piza-Katzer (surgeon in chief and professor at the dept. of plastic surgery of the Innsbruck University Clinic, Austria) showed astonishing results of shock wave therapy after burning lesions of humeral skin and of a randomized animal trial regarding ischemic skin lesions and shock wave therapy and Wolfgang Schaden (traumatologist at the Meidlinger Trauma Center Wien, Austria) demonstrated the results of a pilot study concerning shock wave therapy and skin ulcers of different reasons (diabetic ulcers, posttraumatic delayed skin healing etc.). There have been reports in the daily news at the national broadcast channel and in the news papers and reports at the scientific programmes.

As at the last ISMST congresses we could organize sessions with veterinarian papers, mainly US American studies with horses have been presented. Shock wave therapy in that field is obviously increasing. It is one of the advantages of the ISMST as a society, that we held it open for everyone who is interested in shock waves, so we have a mixed composition of members of all fields of application - physicians from all different disciplines, veterinarians, clinical investigators, basic researchers, manufacturers and distributors. The scientific level of the presented papers has risen over the years.

The 8th ISMST Congress has been held together with the 5th meeting of the German speaking shock wave societies (5. Dreiländertreffen der Österreichischen, Schweizerischen und Deutschen Gesellschaften für Extrakorporale Stoßwellentherapie). The most important society in that group is the DIGEST (Deutschsprachige Internationale Gesellschaft für Extrakorporale Stoßwellentherapie), and this society provided an award for the best paper regarding shock wave therapy. The last years the first two awards have been presented to Markus Maier and Ludger Gerdesmeyer. This year it was a big honour for the ISMST, that the ceremony of awarding has taken place at the opening ceremony of the ISMST congress and it was presented to Jan-Dirk Rompe (Germany) for his clinical study about differences in outcome of ESWT regarding treatment with or without local anaesthetics. At the DIGEST member's meeting in Vienna the assembly has voted for calling for participants for that DIGEST award also thru the ISMST correspondence. This is a sign for good relations between the societies and we hope very much to keep the contact as close as it is now.

Besides the scientific programme the social events have been of good acceptance. special guests have been invited for a presidential dinner to celebrate the 8th birthday of the ISMST founded 1997 in Vienna. A reception at the city hall of Vienna as an invitation of the Lord Mayor of Vienna took place on Monday, May 30th, 2005. The next day we celebrated the society evening in best mood, beginning the event with a street car drive to a typical Viennese winery (25 minutes walk after the street car drive thru the city, than a magnificent view over Vienna, Viennese winery atmosphere with typical music and wine and food and lots of scientific discussions, friendly talks and singing and laughing!). The whole meeting was characterized by the excellent communication, which is the main interest of the ISMST. So as organizers we are happy that the congress was a big success.

We are convinced that this society is growing and we will get members of other disciplines, we are already discussing the name of the society because of the new fields of shock wave therapy which are not only musculoskeletal. The development will continue! We are very much looking forward to the next meeting, the 9th ISMST Congress in Rio de Janeiro from April 20th to April 23rd, 2006 (www.ismst.com).

CORRESPONDING ADDRESS:

Dr. Vinzenz Auersperg
Orthopaedic Department of the General Hospital Linz (AKH Linz)
Krankenhausstrasse 9
A-4020 Linz
Austria - Europe
vinzenz.auersperg@akh.linz.at
or vinzenz@auersperg.cc

Dinner party.

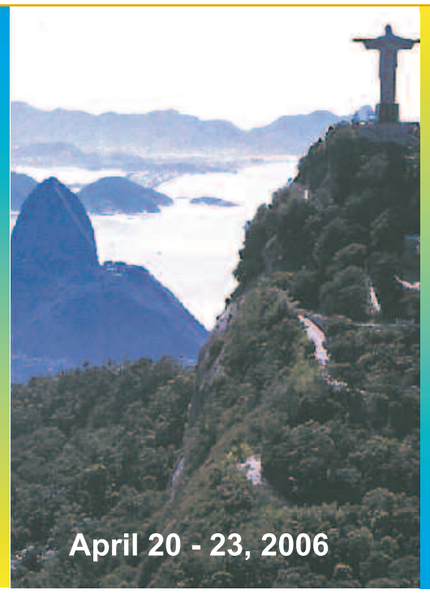
Groups from Brazil and Twain and Dr Richard Thiele.

Ana Claudia Souza and Wolfgang Schaden.

9th Congress International

of the International Society for Musculoskeletal Shockwave Therapy

Rio de Janeiro - Brazil



April 20 - 23, 2006

Dear Colleagues,

The Organizing Committee has already been managing to welcome all the colleagues and international members from the 53 countries that belong to the ISMST. We have been doing our best to provide a comfortable, as well as safe, Congress which will be held where the Pan-American Games of 2007 will take place - Barra da Tijuca.

We are honored and motivated with the mission to host, for the first time in Latin American, the biggest event of the Shockwave Therapy applied to the Musculoskeletal System, whose accomplishment has been considered to be a great challenge. We hope to join both scientific activities and the possibility of enjoying this Wonderful City, and then, make this event one of the warmest ever. Your presence will be an honor to us and to the city of Rio de Janeiro. See you in 2006!

Dr. Souza, Ana Claudia.

President of the 9th International Congress of the ISMST and Organizing Committee.

INTERNATIONAL SOCIETY FOR MUSCULOSKELETAL SHOCKWAVE THERAPY

ISMST

International Society for Musculoskeletal Shockwave Therapy

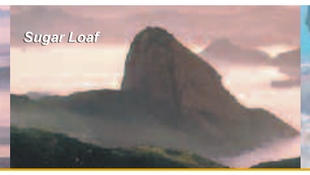
RIO DE JANEIRO 2006

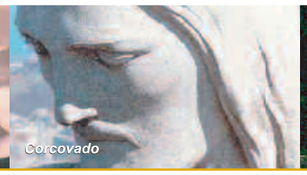
Oficial Travel Agency

AGÊNCIA ROXY DE TURISMO LTDA desde 1948

Phone: + 55 21 3584-0141
Fax: + 55 21 2524-7648
fabio@roxytravel.com.br

www.ismst.com





Biological Mechanism of Musculoskeletal Shockwaves

Ching-Jen Wang, MD[1], Feng-Sheng Wang, PhD[2] and Kuender D. Yang, MD, PhD[2]

The Department of Orthopedic Surgery[1] and Medical Research[2] Chang Gung Memorial Hospital at Kaohsiung Taiwan.

Abstract

These studies were conducted to investigate the biological mechanism of musculoskeletal shockwaves. The investigations were independently performed in tendon and bone, and at the tendon-bone interface in rabbits. The study limbs were treated with shockwaves, whereas the control limbs received sham treatment with no shockwave. The evaluations included histomorphological examination, biomechanical analysis and immunohistochemical assessments of angiogenic growth indicators including endothelial nitric oxide synthase (eNOS), vessel endothelial growth factor (VEGF), bone morphological protein (BMP-2) and proliferating cell nuclear antigen (PCNA).

The results showed higher bone strength and bone mass, and better tensile strength of the graft at tendon-bone interface in the shockwave group than the control group. Furthermore, shockwave treatment significantly induced the ingrowth of neovascularization associated with increased expressions of angiogenic growth indicators in tendon and bone, and at the tendon-bone interface as compared with the control. The effects of shock waves appeared to be time-dependent as well as being dose-dependent.

In conclusion, extracorporeal shock waves produced consistent biological effects in tendon and bone, and at the tendon-bone interface. The biological mechanism of musculoskeletal shockwaves appeared to stimulate the expressions of angiogenic growth factors and induce the ingrowth of neovascularization. Neovascularization may play a role in the improvement of blood supply and healing of tendon and bone.

Introduction

Extracorporeal shock wave has been shown to be effective for certain orthopedic conditions including non-union of long bone fracture,[1,2,3,4] calcifying tendonitis of the shoulder,[5,6,7,8,9] lateral epicondylitis of the elbow,[10,11,12,13] proximal plantar fasciitis[14,15,16] and Achilles tendonitis.[17] In animal experiments, shockwaves also showed positive effects in promoting bone healing.[18,19,20,21] However, the exact mechanism of shockwave in musculoskeletal disorders remains unknown. The results of animal experiments demonstrated that shockwaves induced neovascularization at the tendon-bone junction.[22,23] We hypothesized that physical shockwaves might induce biological effects that lead to healing of tendons and bone. The purposes of the studies were to investigate the biological effects of shockwaves in tendon, bone and tendon-bone interface and to elucidate the biological mechanism of musculoskeletal shockwaves.

Materials and Methods

The approval of The Institutional Review Board was obtained. These studies were performed under the guidelines and the care and use of animals in research.

I. Experimental study in tendon

Fifty New Zealand white rabbits of 12 months old with body weight ranging from 2.5 to 3.5 Kg were used in this study. The right limbs (study side) received shockwave treatment to the Achilles tendon near the insertion to heel bone, while the left limbs (control side) received sham treatment with no shock waves. The source of shockwave was from an electrohydraulic OssaTron device (High Medical Technology, Kreuzlingen, Switzerland). The shockwave tube was focused on the Achilles tendon near the insertion, and the depth of the treatment was determined with the control guide of the machine and confirmed with C-arm image. Each of the study limbs received a single treatment of shockwave with 500 impulses at 14 kV (equivalent to 0.18 mJ/mm^2). The shockwave dosage so selected was based on our previous experiences in animal studies.[21,22,23] The sham treatment was performed on the left limbs (control side) using a dummy electrode that did not generate acoustic waves with the impulses.

Histomorphological examination

Biopsies of the Achilles tendon-bone unit were performed in 0, 1, 4, 8 and 12 weeks with 10 rabbits at each time interval with the first biopsy obtained in 24 hours after shockwave application. The decalcified specimens were sectioned and stained with hematoxylin-eosin stain. The tissue distributions and the number of new blood vessels including capillary and muscularized vessel were examined microscopically.

Immunohistochemistry analysis

The angiogenic growth markers including vessel endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) were examined to confirm the neovascularization, and proliferating cell nuclear antigen (PCNA) was chosen to reflect endothelial cell proliferation with immunohistochemistry stains.[24,25,26] The vessels showing positive VEGF expression and cells displaying positive PCNA and eNOS expressions were counted microscopically and the numbers of cells and tissues with positive expression were quantitatively assessed.

Results of biological response in tendon

The results of eNOS, VEGF and PCNA expressions and the number of neo-vessel of the study and the control sides are summarized in **Table 1**. In the study side, a significant increase in the number of neo-vessels was noted in 4 to 12 weeks, whereas no increase of neo-vessels was noted in the control side, and the difference was statistically significant. It appeared that the ingrowth of neo-vessels after shockwave treatment was time dependent. In the study side, significant increases of eNOS, VEGF and PCNA were noted in as early as one week and lasted for 8 weeks before they declined to normal at 12 weeks, except PCNA increase lasted until 12 weeks (**Fig. 1**). In the control side, however, no significant changes in eNOS, VEGF and PCNA expressions were noted, and the differences between the study and control sides were statistically

Table 1. The results of eNOS, VEGF and PCNA expression and the number of neo-vessels in tendon.[23]

Time	Control (N=50) Mean ± SD	Shockwave (N=50) Mean ± SD	P-value
0- week (N=10)			
eNOS	112 ± 19	104 ± 21	0.57
VEGF	14 ± 3	12 ± 4	0.94
PCNA	145 ± 21	132 ± 24	0.75
Neo-vessel	22 ± 3	24 ± 4	0.93
1-week (N=10)			
eNOS	124 ± 21	293 ± 31	<0.001
VEGF	17 ± 4	33 ± 5	0.0068
PCNA	155 ± 37	332 ± 28	0.021
Neo-vessel	24 ± 4	26 ± 5	0.95
4-week (N=10)			
eNOS	131 ± 24	344 ± 32	<0.001
VEGF	14 ± 5	36 ± 6	0.0018
PCNA	134 ± 38	320 ± 32	0.011
Neo-vessel	22 ± 5	42 ± 4	0.024
8-week (N=10)			
eNOS	138 ± 26	265 ± 45	0.016
VEGF	15 ± 4	28 ± 4	0.034
PCNA	167 ± 33	312 ± 36	0.024
Neo-vessel	24 ± 5	40 ± 5	0.021
12-week (N=10)			
eNOS	136 ± 21	189 ± 42	0.71
VEGF	17 ± 5	16 ± 4	0.84
PCNA	154 ± 21	280 ± 28	0.034
Neo-vessel	25 ± 6	42 ± 4	0.017

P-values: Comparison of the control with the shock wave side was based on Mann-Whitney test. (40x magnification)

significant. It appeared that shockwaves stimulated the early release of eNOS, VEGF and PCNA expressions, and subsequent ingrowth of neo-vessels.

II. Experimental study in bone

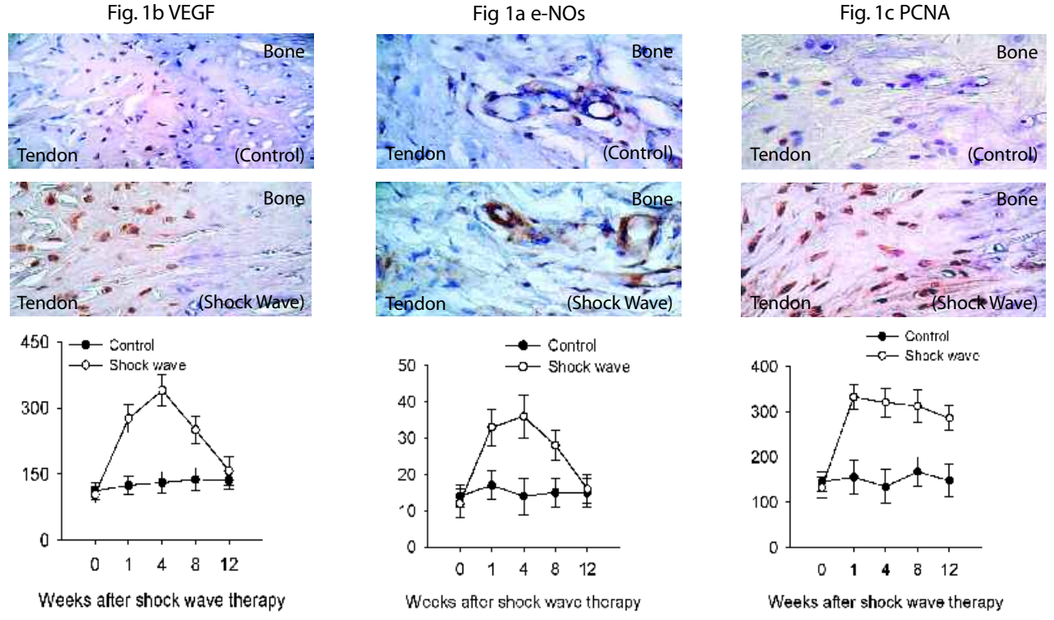
Twenty-four New Zealand white rabbits of 12 months old with body weight ranging from 2.7 kg to 3.6 kg were used in this study. A 1.5 mm Kirchnur pin was inserted retrograde into the canal of the femur through a mini-arthrotomy of the knee. A closed fracture of the right femur was created with a three-point bend method and was confirmed with radiographs. The rabbits were randomly divided into three groups with eight rabbits in each group. The first group (the control) received sham treatment with no shock wave. The second group received low-energy shock wave with 2000 impulses at 14 kV (equivalent to 0.18 mJ/mm^2 energy flux density). The third group received high-energy shock wave with 4000 impulses at 14 KV. Shock waves were applied in one week after the operation when the surgical wounds had healed. The location of the fracture site and the depth of the treatment were confirmed with the control guide of the machine and C-arm imaging. The sham treatment was performed with a dummy electrode that did not generate acoustic waves with the impulses.

Radiographs of the right femur in A-P and lateral views were performed in[1,4,8] and 12 weeks. The fracture healing was evaluated with clinical assessment and confirmed with radiographic examination.

Biomechanical examination

The animals were sacrificed at 12 weeks, and a 5-cm long femur bone including the callus was harvested. The specimens were subject to biomechanical testing on Material Testing System (MTS, Minneapolis, MN) including peak load, peak stress and modulus of elasticity. The biomechanical testing was similarly performed in high-energy, low-energy and control groups.

Fig. 1



In the study group, significant increases of eNOS, VEGF and PCNA noted in as early as one week and lasted for 8 weeks before they declined to normal at 12 weeks, except PCNA increase lasted until 12 weeks on immunohistochemical stains . In the control side, however, no significant changes in eNOS, VEGF and PCNA expressions were noted, and the differences between the study and control sides were statistically significant.[23]

Histomorphological examination

After biomechanical testing, the specimens were decalcified and sectioned and subject to hematoxylin-eosin, alcian blue or alizarin red stains (Sigma Chemicals Inc, St. Louis, MO, USA) for the purpose of distinguishing fibrous tissue, cartilaginous and bony tissues within the region of interest.

Immunohistochemical examination

The angiogenic activities including eNOS, VEGF, BMP-2 and PCNA were examined with immunohistochemistry stains for verification of neo-vessels. The specimens were immunostained for eNOS, VEGF, BMP-2 and PCNA (Santa Cruz Biotechnolog Inc, CA, USA). An antibody against von Willebrand factor (vWF) was used to identify the immunolocalization of neo-vessels in the fracture sites. The number of positive immuno-labeled cells and total cells in each area were counted and the percentage of positive labeled cells was calculated.

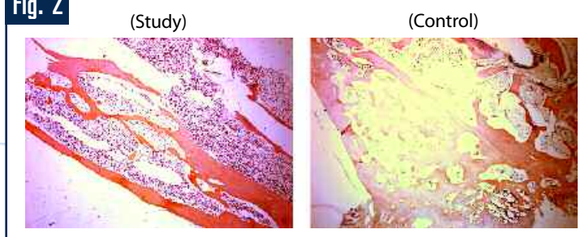
Results of biological response in bone

The histomorphological features showed that high-energy shock waves produced significantly more cortical bone, less fibrous tissue and comparable woven bone than the control and low-energy shock waves (**Fig. 2**). The results of low-energy shock wave did not differ significantly from the control group.

The results of biomechanical study showed that high-energy shock waves demonstrated better bone strength including peak load, peak stress and modulus of elasticity than low-energy shock wave and the control (**Fig. 3**). The low-energy shock waves showed comparable results as compared with the control.

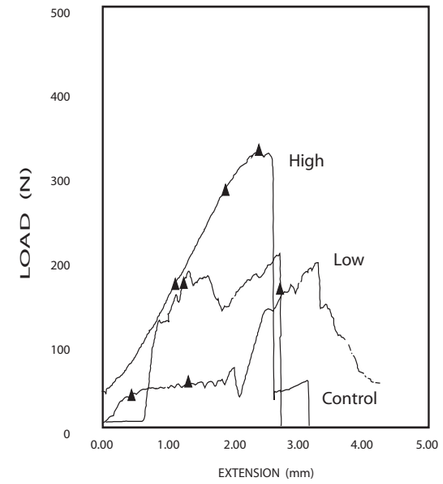
The results of positive eNOS, BMP-2, VEGF and PCNA immunostained cells and the numbers of neo-vessels in the fracture sites of the control, low- and high-energy groups are summarized in **Table 2**. The numbers of neo-vessels and cells with positive eNOS, BMP-2, VEGF and PCNA expressions are significantly higher in high-energy shockwave group than the control and low-energy groups (**Fig. 4**). The data of the low-energy group did not differ significantly from the control group. The biological effects of shockwaves appeared to be dose-dependent.

Fig. 2



Histomorphology showed that high-energy shock waves produced significantly more cortical bone, less fibrous tissue and comparable woven bone than the control and low-energy shock waves.[39]

Fig. 3



Biomechanical testing showed that high-energy shock waves demonstrated better bone strength including peak load, peak stress and modulus of elasticity than low-energy shock waves and the control. The low-energy shock waves showed comparable results as compared with the control.[39]

Table 2. The results of positive eNOS, VEGF, BMP and PCNA immunostained cells and the number of neo-vessels in bone.

Shock waves	Control	Low-energy	High-energy
Neo-vessel and growth indicator	N = 8 Mean ± SD	N = 8 Mean ± SD	N = 8 Mean ± SD
BMP-2	211 ± 21	207 ± 28	348 ± 19
P-value 1		0.74	0.015
P-value 2			0.026
eNOS	179 ± 16	192 ± 18	272 ± 21
P-value 1		0.89	0.026
P-value 2			0.014
VEGF	168 ± 20	186 ± 20	257 ± 21
P-value 1		0.62	0.036
P-value 2			0.024
PCNA	196 ± 26	213 ± 18	306 ± 21
P-value 1		0.87	< 0.01
P-value 2			0.017
Neo-vessels	37 ± 10	43 ± 12	78 ± 17
P-value 1		0.72	0.012
P-value 2			0.006

The data were analyzed using a general linear model followed by a Duncan's multiple range of test to determine the significance between treatments. (40x magnification)

P-value 1: comparison of the control with low- and high-energy groups.

P-value 2: comparison of low-energy with high-energy groups.

III. Experimental study in tendon-bone interface

Thirty-six New Zealand white rabbits of 12 months old with body weight ranging from 2.79 Kg to 3.65 Kg were used in this study. Arthrotomy of the knee was carried out and the anterior cruciate ligament (ACL) was excised. The long digital extensor tendon was dissected off distally at the musculotendinous junction while the proximal end was left intact. A tibia tunnel was created with a graft size-matched drill bit. The distal end of the graft was pulled through the tibia tunnel to complete ACL reconstruction.

Shockwave application

The left knees received sham treatment with no shock wave, and were used as the control group. The right knees received shockwave treatment immediately after surgery, and were regarded as the study group. The shockwave tube was focused on the mid-portion of the tibia tunnel with the control guide of the device, and the depth was estimated clinically and determined with an ultrasound guide. Each knee was treated with 500 impulses of shockwaves at 14 kV (equivalent to 0.18 mJ/mm^2) to the right knee. In sham treatment, a dummy electrode was used that no acoustic waves were generated with the impulses.

Histomorphological Studies

Twenty-four rabbits were sacrificed at different time intervals with 4 rabbits each at 1, 2, 4, 8, 12 and 24 weeks. The central portion of the proximal tibia including the tendon graft was harvested. The specimens were decalcified, sectioned and stained with hematoxylin-eosin stain. The distributions of the tissues surrounding tendon graft and the bonding of trabecular bone to tendon were examined microscopically.

Biomechanical examination

Twelve rabbits were sacrificed at 12 and 24 weeks with 6 rabbits at each time interval. The ligament structures of the knee were removed and only the ACL graft was retained. The tensile strength of the graft was measured with slow load distraction curve on Material Testing Machine (MTS, Minneapolis, MN). The pullout strength, the failure load and the modes of failure were analyzed.

Immunohistochemical examination

The decalcified specimens were cut into sections in longitudinal and axial directions. Sections were immunostained for eNOS, VEGF, BMP-2 and PCNA (Santa Cruz Biotechnolog Inc, CA, USA) for the purpose of identifying angiogenic growth indicators. An antibody against von Willebrand factor (vWF) was used to identify the immunolocalization of neo-vessels. The numbers with positive expression were quantitatively assessed.

Results of biological response in tendon-bone interface

The trabecular bone in the surrounding tissues of the tendon graft increased significantly with time in the study group ($P < 0.05$), whereas, the changes in the control group were statistically not significant ($P > 0.05$). The difference in the amount of trabecular bone around the tendon graft between the study and control groups was statistically significant after 4 weeks. The bonding between tendon and bone was much more intimate in the study group than the control group, and the difference in the percentage of bonding between tendon and bone was statistically significant between the study and control groups ($P < 0.05$) (**Fig. 5**).

The biomechanical testing showed that higher tensile strength of the graft and better pullout failure load noted in the shockwave group than the control group (**Fig. 6**).

The results of eNOS, VEGF, PCNA and BMP-2 expressions and the number of neo-vessels at the tendon-bone interface at different time intervals are summarized in **Table 3**. The numbers of neo-vessels and the cells with positive immunostain are significantly higher in the shockwave group than the control group, and the difference was statistically significant at different time intervals (**Fig. 7**).

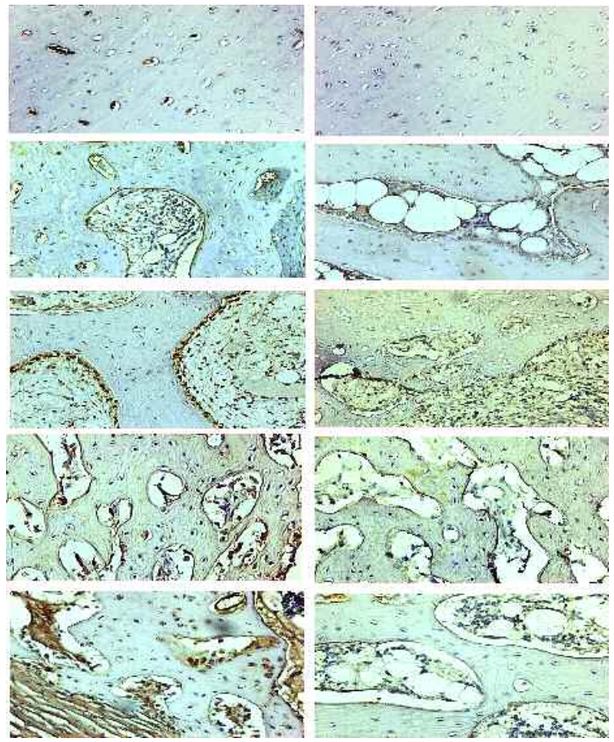
Discussion

Some authors speculated that shockwaves relieved pain due to insertional tendinopathy by hyper-stimulation analgesia and increase of pain threshold.[28] Other authors hypothesized the mechanism of microfracture including micro-disruption of avascular or minimally vascular tissue to encourage revascularization and the recruitment of appropriate stem cells conductive to bone healing.[27,28] However, there are insufficient data to scientifically substantiate either theory concerning the mechanism of shockwaves in musculoskeletal disorders. Many recent studies in animal experiments demonstrated the modulation of shockwave including neovascularization, osteogenic differentiation of mesenchymal stem cell and release of osteogenic and

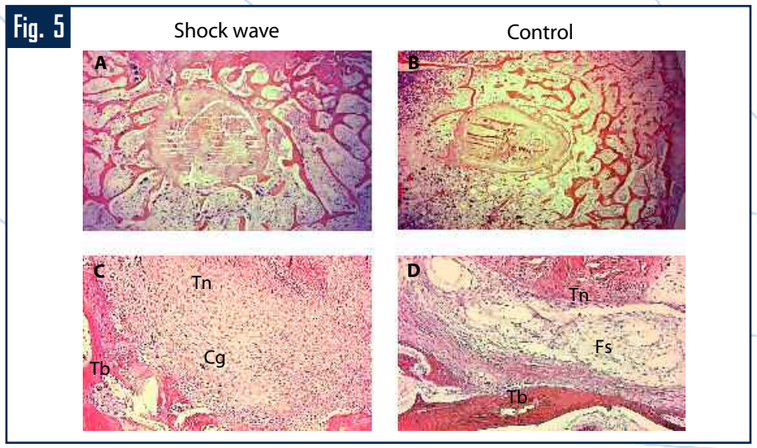
Table 3. The results of eNOS, VEGF-A, PCNA and BMP-2 expressions and the number of neo-vessels in tendon-bone interface.

Time	Growth indicator	Shockwave Mean ± SD	Control Mean ± SD	P-value
1-week (N=3)	eNOS	256±21	112±18	<0.001
	VEGF-A	246±36	228±25	0.82
	PCNA	122±15	123±17	0.63
	BMP-2	89±11	94±13	0.58
	Neo-vessels	47±9	41±2	0.534
2-weeks (N=3)	eNOS	224±24	106±18	0.006
	VEGF-A	389±42	254±27	0.014
	PCNA	234±21	138±19	0.023
	BMP-2	143±22	98±17	0.014
	Neo-vessels	53±12	46±13	0.619
4-weeks (N=3)	eNOS	202±20	108±21	0.016
	VEGF-A	432±41	268±32	0.002
	PCNA	278±26	143±21	0.016
	BMP-2	184±24	104±16	0.007
	Neo-vessels	82±14	52±11	0.017
8-weeks (N=3)	eNOS	142±18	122±25	0.14
	VEGF-A	452±37	276±28	0.004
	PCNA	316±23	149±19	0.022
	BMP-2	212±21	98±15	<0.001
	Neo-vessels	93±15	47±9	<0.01
12-weeks (N=6)	eNOS	123±19	108±23	0.57
	VEGF	463±26	284±26	0.013
	PCNA	308±21	158±25	0.017
	BMP-2	168±24	106±18	0.023
	Neo-vessels	87±14	44±12	0.0085
24-weeks (N=6)	eNOS	132±23	98±19	0.68
	VEGF	476±31	271±25	<0.001
	PCNA	312±28	154±17	<0.001
	BMP-2	152±27	115±16	0.026
	Neo-vessels	86±12	47±12	0.0046

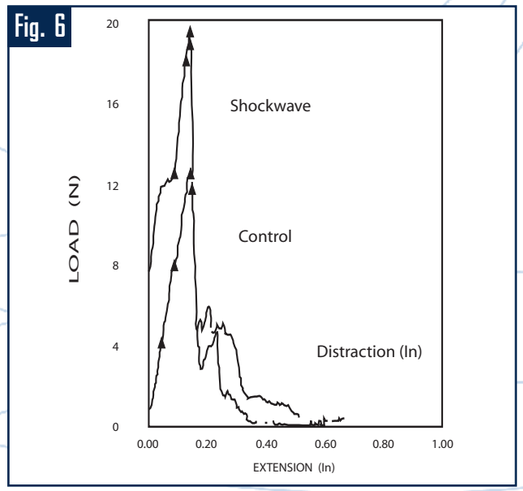
P-values were based on Mann-Whitney test. (40x magnification)



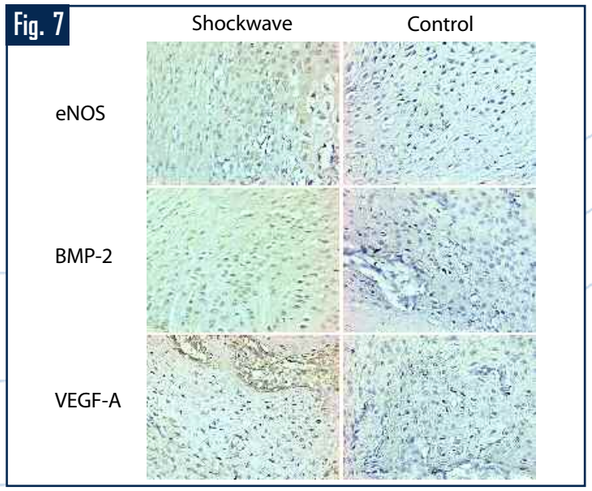
The numbers of neo-vessels and cells with positive eNOS, BMP-2, VEGF and PCNA expressions are significantly higher in high-energy shock wave group than the control group.



The trabecular bone surrounding the tendon graft increased significantly in the shock wave group as compared with the control group. The bonding between tendon and bone was much more intimate in the study group than the control.[37]



Biomechanical testing showed higher tensile strength and better pull-out failure load in the shock wave group than the control group.[37]



The numbers cells with positive immunostain for eNOS, BMP-2 and VEGF-A at the tendon-bone interface are significantly higher in the shock wave group than the control group.[37]

angiogenic growth factors.[22,23,29,37] Therefore, extracorporeal shockwaves produced effects of tissue regeneration and/or repair in musculoskeletal tissues, rather than a mechanical disintegration.

Many studies demonstrated that over-expressions of eNOS and VEGF induced angiogenesis.[24,25] The results of the current studies demonstrated for the first time that mechanical shockwaves stimulated the ingrowth of neovascularization associated with increased expressions of angiogenic growth markers including eNOS, VEGF and PCNA in tendon, bone and tendon-bone interface. Neovascularization may play a role to improve blood supply and healing of tendon and bone. Rompe et al[38] reported a dose related effects of shockwave on rabbit tendon Achilles. Wang et al[39] demonstrated that shockwave treatment showed dose-dependent enhancement of bone mass and bone strength after fracture of the femur. The results of these studies showed that the effect of shockwave in musculoskeletal tissues appeared to be time-dependent as well as being dose-dependant. Therefore, it seemed likely that physical shockwaves raised the mechanotransduction and converted into biological signals that lead to a cascade of biological responses in tendon, bone and tendon-bone interface (**Fig. 8**).

Conclusion

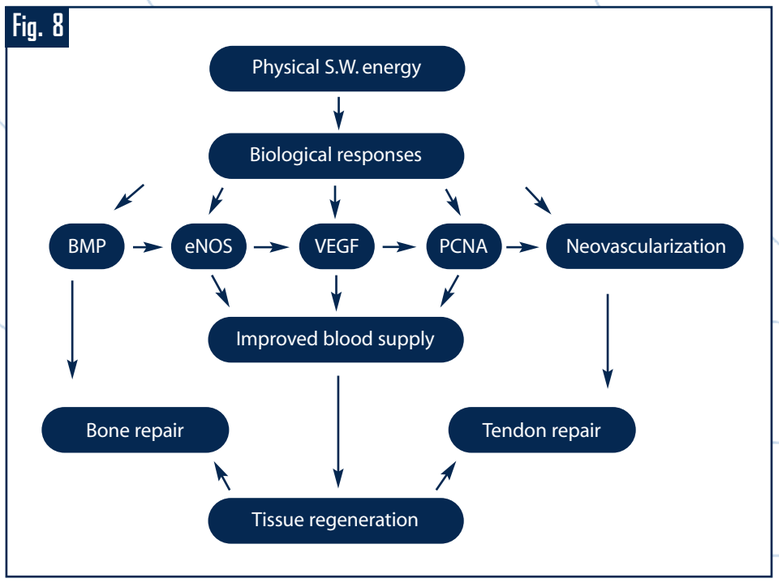
The biological mechanism of musculoskeletal shockwaves appeared to initially stimulate the expressions of angiogenic growth factors, and subsequently the ingrowth of neovascularization and improvement in blood supply that lead to repair of tendon and bone. Musculoskeletal shockwaves produced consistent biological effects in tendon and bone and at the tendon-bone interface. In contrast to lithotripsy where shockwaves are used to disintegrate urolithiasis, shockwaves in orthopedics (orthotripsy) are not been used to disintegrate tissues, but rather to microscopically cause interstitial and extracellular biological effects including tissue regeneration.

Acknowledgement

These studies were partially or totally supported by grants. The sources of grants are from Chang Gung Research Fund (CMRP 83001) and National Science Council (NSC91-2314-B-182A-068). No fund was received or will be received from a commercial party directly or indirectly related to the subjects of this article.

The authors like to thank Ya-Zu Yang, Yi-Chi Sun and Ya-Hsieh Chuang for their technical assistances and collection of data in the studies.

Fig. 8



A proposed cascade of biological mechanism of extracorporeal shock waves in musculoskeletal tissues.

References

1. Haupt G. Use of extracorporeal shock wave therapy in the treatment of pseudoarthrodesis, tendinopathy and orthopaedic disease. J Urology 1997; 158:4-11.
2. Rompe JD, Rosendahl T, Schöllner C, et al. High-energy extracorporeal shock wave treatment of nonunions. Clin Orthop 2001; 387: 102-111.
3. Schaden W, Fischer A and Sailler A. Extracorporeal shock wave therapy of nonunion or delayed osseous union. Clin Orthop 2001; 387: 90-94.
4. Wang CJ, Chen HS, Chen CE, et al. Treatment of nonunions of long bone fractures with shock waves. Clin Orthop 2001; 387: 95-101.
5. Loew M, Daecke W, Kuznierczak D, et al. Shock-wave therapy is effective for chronic calcifying tendonitis of the shoulder. J Bone Joint Surg 1999; 81B: 863-867.
6. Rompe JD, Rumler F, Hopf C, et al. Extracorporeal shock wave therapy for calcifying tendinitis of the shoulder. Clin Orthop 1995; 321:196-201.
7. Speed CA, Richards C, Nichols D, Burnet S, Wiles JT, Humphrey H, Hazlemann BL. Extracorporeal shock wave therapy for tendonitis of the rotator cuff. A double-blind, randomized, controlled trial. J Bone Joint Surg. (Br) 2002; 84: 509-12
8. Wang CJ, Ko JY, Chen HS. Treatment of calcifying tendonitis of the shoulder with shock wave therapy. Clin Orthop 2001;387: 83-89.
9. Wang CJ, Yang KD, Wang FS. Shock wave therapy for calcifying tendinitis of the shoulder. A two- to four-year follow-up. Am J Sports Med 2003; 31(3):425-30.
10. Hammer DS, Rupp S, Ensslin S, et al. Extracorporeal shock wave therapy in patients with tennis elbow and painful heel. Arch Orthop Trauma Surg 2000; 120:304-307.
11. Ko JY, Chen HS, Chen LM. Treatment of lateral epicondylitis of the elbow with shock waves. Clin Orthop 2001; 387: 60-67.
12. Rompe JD, Hopf C, Kullmer K, et al. Analgesic effect of extracorporeal shock wave therapy on chronic tennis elbow, J Bone Joint Surg 1996; 78B: 233-237.
13. Speed CA, Nichols D, Richards C, Humphrey SH, Wiles JT, Burnet S, Hazlemann BL. Extracorporeal shock wave therapy for lateral epicondylitis - a double-blind, randomized, controlled trial. J Orthop Res. 2002; 20: 895-8.
14. Chen HS, Chen LM, Huang TW. Treat-ment of painful heel syndrome with shock waves. Clin Orthop 2001; 387: 41-46.
15. Ogden JA, Alvarez R, Levitt R, et al. Shock wave therapy for chronic proximal plantar fasciitis. Clin Orthop 2001; 387:47-59.
16. Rompe JD, Hopf C, Nafe B, et al. Low-energy extracorporeal shock wave therapy for painful heel: A prospective controlled single-blind study. Arch Orthop Trauma Surg 1996; 115:75-79.
17. Perlick L, Schifmann R, Kraft CN, Wallny T, Diedrich O. Extracorporeal shock wave treatment of the Achilles tendonitis: Experimental and preliminary clinical results. Z Orthop Ihre Grenzgeb 2002; 140(3): 275-80.
18. Delius M, Draenert K, Al Diek Y, et al. Biological effect of shockwave: In vivo effect of high-energy pulses on rabbit bone. Ultrasound Med Biol 1995; 21:1219-1225.
19. Johannes EJ, Kaulesar-Sukul DM, Metura E, et al. High-energy shock waves for the treatment of nonunions: An experiment on dogs. J Surg Res 1994; 57:246-254.
20. Kaulesar Sukul DM. Johannes EJ. Pierik EG. van Eijck GJ. Kristelijn MJ. The effect of high-energy shock waves focused on cortical bone: An in vitro study. J Surg Res 1993; 54: 46-51.
21. Wang CJ, Huang HY, Chen HH, et al. Effect of shock wave therapy on acute fractures of the tibia. A study in a dog model. Clin Orthop 2001;387: 112-118.
22. Wang CJ, Huang HY, Pai CH: Shock wave therapy enhanced neovascular-ization at the tendon-bond junction: an experiment in dogs. J Foot Ankle Surg 2002; 41: 16-22.
23. Wang CJ, Yang KD, Wang FS, Huang CC, Yang LJ. Shock wave induces neovascularization at the tendon-bone junction. A study in rabbits. J Orthop Res 2003; 21:984-989.
24. Babaei S, Stewart DJ. Overexpression of endothelial NO synthase induces angiogenesis in a co-culture model. Cardiovascular Res. 2002; 55: 190-200.
25. Spyridopoulos I, Luedeman C, Chen D, Kearney M, Murohara T, Principe N, Isner M, Losordo DW. Divergence of angiogenesis and vascular permeability signaling by VEGF: inhibition of protein kinase C suppresses VEGF-induced angiogenesis, but promotes VEGF-induced NO-dependent vascular permeability. Arteriosclero, Thrombo and Vas Biol 2002; 22: 901-6.
26. Nagashima M, Tanaka H, Takahashi A, Tanaka K, Ishiwata T, Asano G, Yoshino S. Study of the mechanism involved in angiogenesis and synovial cell proliferation in human synovial tissues of patients with rheumatoid arthritis using SCID mice. Lab Invest 2002; 82(8): 981-8.
27. Ogden JA, Toth -Kischkat A, Schultheiss R. Principles of shock wave therapy. Clin Orthop 2001; 387: 8-17.
28. Thiel M: Application of shock waves in medicine. Clin Orthop 2001; 387: 18-21.
29. McCormack D, Lane H, McElwain J. The osteogenic potential of extracor-poreal shock wave therapy: An in-vivo study. Ir J Med Sci 1996; 165:20-22.
30. Maier M, Milz S, Wirtz DC, Rompe JD, Schmitz C. Basic research of applying extracorporeal shockwaves on the musculoskeletal system. An assess-ment of current status. Orthop 2002; 31: 667-77.
31. McCormack D, Lane H, McElwain J. The osteogenic potential of extracor-poreal shock wave therapy: An in vivo study. Irish J Med Sci 1996; 165: 20-22.
32. Wang FS, Wang CJ, Sheen-Chen SM et al. Superoxide mediates shock wave induction of RRK-dependent osteogenic transcription factor (CBFA 1) and mesenchymal cells differentiation toward osteoprogenitors. J Biol Chem 2002; 277: 10931-7
33. Wang FS, Yang KD, Wang CJ, et al. Extracorporeal shock wave promotes bone marrow stromal cell growth and differentiation toward osteoprogenitors associated with TGF-b 1 induction. J Bone Joint Surg 2002; 84B: 457-61.
34. Wang FS, Wang CJ, Huang HC, et al. Physical shock wave mediates membrane hyperpolarization and Ras activation for osteogenesis in human bone marrow stromal cells. Biochemical Biophysical Research Communications 2001; 287: 648-655.
35. Wang FS, Yang KD, Kuo YR, Wang CJ, Huang HJ, Chen YJ. Temporal and spatial expression of bone morphogenetic proteins in extracorporeal shock wave-promoted healing of fracture defect. Bone 2003; 32:387-396.
36. Yang C, Heston WDW, Gulati S, Fair WR. The effect of high-energy shock waves (HESW) on human bone marrow. Urol Res 1988; 16:427-42.
37. Wang CJ, Wang FS, Yang KD, Weng LS, Sun YC, Yang YL. The effect of shock wave treatment at the tendon-bone interface - A histomorphological and biomechanical study in rabbits. J Orthop Res 2004 (In press).
38. Rompe JD, Kirkpatrick CJ, Küllmer K, et al. Dose related effects of shock waves on rabbit tendon Achilles. A sonographic and histological study. J Bone Joint Surg 1998; 80B: 546-552.
39. Wang CJ, Yang KD, Wang FS, Hsu CC, Chen HS. Shock wave treatment shows dose-dependent enhancement of bone mass and bone strength after fracture of the femur. Bone 2004; 34:225-230.

REPRINT REQUEST AND CORRESPONDENCE TO:

Ching-Jen Wang, M.D.
Department of Orthopedic Surgery Chang Gung Memorial Hospital at Kaohsiung
123 Ta-Pei Road, Niao-Sung Hsiang Kaohsiung, Taiwan 833
Tel: 886-7-733-5279; Fax: 886-7-733-5515
E-mail: w281211@adm.cgmh.org.tw

Running title: Biological mechanism of musculoskeletal shockwaves.

Effects of extracorporeal shock wave treatment on equine tendon healing

Ana Liz G. Alves, DVM, PhD; Brunna Patrícia Almeida da Fonseca DVM, Ms; Renée L. Amorim, DVM, PhD; Armen Thomassian, DVM, PhD; Carlos A. Hussni, DVM, PhD; José Luis M. Nicoletti, DVM, PhD

From the Faculdade de Medicina Veterinária e Zootecnia, São Paulo State University, Botucatu - SP (Caminoto, Alves, Colla, Amorim, Thomassian, Hussni, Nicoletti); Supported by Fundação de Apoio aos Hospitais Veterinários da Unesp (research support foundation of Unesp Veterinary Hospital).

Abstract

In the present study, the effects of the extracorporeal shock wave therapy (ESWT) was assessed in experimental equine tendinitis. Extracorporeal shock wave therapy may stimulate collagen fiber orientation permitting better reorientation of the repair tissue. Ten horses without health problems were used in this experiment. Superficial digital flexor tendinitis was induced in both front limbs of each horse by use of a collagenase injections in each superficial tendon. On the thirtieth day after the collagenase injection, the right front limb of each horse was treated with ESWT (3 treatments at 3-week intervals); the left front limb was not treated (control limb). Periodically during the study, the healing process was monitored ultrasonographically and the proportions of tendons affected with lesions were assessed. On the 120th day of the experiment, biopsy specimens were collected from all tendons for histological evaluation. The present results indicate that ESWT improved scar remodeling and tendon wound collagen maturation.

Key words: Shock wave, healing, tendinitis, equine.

Introduction

Equine tendons are frequently hurt by different mechanisms and the lesions showed degenerative phenomena and inflammatory alterations of different degrees of intensity. The healing of these lesions is often unsuccessful concerning restoration of the morphologic and functional characteristics of the tendon, thereby compromising the future athletic performance or increasing the risk of recurrence of lesions in the affected horses.[1]

Many types of treatments have been used to facilitate healing, but there are currently few treatments that stimulate healing to proceed in a timely manner on a consistent basis.[2,3] As one would suspect by the number of therapies that have been tried, none promote healing in a timely fashion to allow earlier return to normal function. Although long convalescence seems to be the most effective treatment, there is still high relapse when the horse returns to its normal workload.

New treatments such as extracorporeal shock wave therapy (ESWT) represent an option for the treatment of superficial digital flexor tendinitis in horses.[3] The ESWT goal is not just to get horse back to work sooner but to promote a better healing i. e. normal collagen alignment of the tendon.[3,4] The use of ESWT in Veterinary is at the beginning. So far, there is little information about different indications, treatment regimens and long-term results. Recent studies have shown that shock wave induce neovascularization at the tendon-bone junction, which in turn relieves pain and improves tissue regeneration and repair.[5] Results of another recent study suggested that ESWT in horses with suspensory ligament desmitis resulted in increased amounts of collagen fibrils and extracellular matrix components and higher immunoreactivity for TGF≤-1 (which may possibly represent increased activity of fibroblasts) in affected ligaments.[6] Few controlled studies have been carried out to investigate the experimental use of the extracorporeal shock waves in horses. The purpose of this study was to evaluate the effects of ESWT on affected tendons of horses with experimentally induced superficial digital flexor tendinitis using ultrasonographic and histological techniques.

Materials and Methods

This study was approved by the Ethics in Animal Experimentation Committee of Unesp-Botucatu. Ten adult horses (5 males and 5 females) were included in this study. The animals were clinically healthy adult Arabian horses on average five years old, specifically selected in terms of a normal locomotor apparatus.

Superficial digital flexor tendinitis was induced in both front limbs of each horse by use the type I collagenase injections, 1ml, 2,5mg/ml, in the middle metacarpal third. For each collagenase treatment, the horses were each sedated with romifidine (0.1 mg/kg, IV) and 2% lidocaine administered in each front limb to provide local anesthesia of the palmar metacarpal and palmar nerves and the skin of the lateral metacarpal region was prepared aseptically. According to ultrasound guidance, collagenase was injected into the lateral region of the metacarpus, reaching the center of the superficial digital flexor tendon, using disposable 30 X 8 hypodermal needle.

Immediately before and 1 week after each collagenase treatment, ultrasonographic evaluation of the collagenase-induced lesions in each front limb was performed using a 7.5-MHz linear transducer. The extent of each lesion was calculated from the measurement of the area of the tendon and the area of the lesion.8 Thirty days after the collagenase treatment, the horses were sedated with romifidine (0.1 mg/kg IV), and were treated in the right front limb with focused ESWT (G1). It involved applications of 500 shocks (5-mm focus) over the lateral aspect, 500 shocks (5-mm focus) over the medial aspect, and 500 shocks (35-mm focus) over the plantar aspect of the scanned region of superficial digital flexor tendon and the energy density was 0.15 mJ/mm^2. Every three weeks for three times, the horses were sedated and their right front limbs were treated with ESWT. The left front limb of each horse (G2) was not treated with ESWT (control group). The progression of the healing process in the ESWT-test and control front limbs were monitored ultrasonographically throughout the study. These evaluations were performed before each of the 3 treatments with ESWT (weeks 4, 7, and 10), and 2 and 4 weeks after the last ESWT (weeks 12 and 14). At the end of the study (120th day after the collagenase treatment), a tendon was biopsied (1.0 X 0.5-cm). After a 12-hour fast, each horse was premedicated with xylazine (1.1 mg/kg, IV) and anesthesia was induced with ketamine (2 mg/kg, IV) and diazepam (0.05 mg/kg, IV) and maintained with continuous IV infusion of guaifenesin (100 mg/kg), ketamine (2 mg/kg), and xylazine (1.1 mg/kg) to submitted to the surgical procedure for a tendon biopsy. Subsequently, horses were recovered from anesthesia and were kept on stall.

Histological analysis. The fragment collected for histology were fixed in 10% buffered formalin and routinely processed. Sections were stained with hematoxylin-eosin and Masson trichrome. Histological analysis was performed under the light microscope by an examiner who was unaware of the group to which the slides belonged. The following features were considered: number and characteristics of fibroblasts, presence of an infiltrate and vascularization, presence of collagen fibers and parallelism of collagen fibers scored on a scale from 0 to 3 (0=absence of parallelism of collagen fibers, 1+ discrete parallelism of collagen fibers, 2= presence of 50% of collagen fibers and 3= total parallelism of collagen fibers.

Statistical analyses were performed by using a Friedman rank point analysis of variance, Wilcoxon test for dependent qualitative samples, and Mann-Whitney tests for independent samples. The level of significance was set at p = 0,05.

Results

Seven days after the collagenase injections, ultrasonographic evaluations revealed 28,02 and 32,70 percentage of the tendon lesions on control and test groups respectively (**table 1**). Test and control groups weren't significantly different eather for ecogenicity or percentage of lesion area, except for the 90 th day. Therefore the fiber alignment scores for test group were increasing faster than for control group which was statistically significant at the end of the experiment.

Few adverse effects such as small areas of hair loss and subsequent development of white hair after treatment.

Discussion

The collagenase model has previously been used for the evaluation of the tendon healing in horses. This model provides a controlled mechanism for paired comparisons and it has been considered an efficient model for tendinitis study.[7,8]

The repair process can be monitored by noninvasive methods, such as ultrasonography or by invasive methods, such as biopsy of tendons for histologic examination, allowing evaluation for the cellularity and the degree of disorganization of the extracellular matrix.[9]

In horses with collagenase-induced superficial digital flexor tendinitis used in the present study, ultrasonographic evaluations revealed that treatment of affected tendons with ESWT had decreased the mean percentage lesion on 90th and 120th days more than in control group and better ecogenicity score on 60th and 90th than control group. Our data corroborate from findings of other studies6,10 as to the use of ESWT in horses with collagenase-induced suspensory ligament desmitis, except that they had significant differences.

The mean fiber alignment ultrasonography score differed significantly between test and control groups. The longitudinal tendon fiber alignment occurred on ESWT group (G1) is an important parameter to return the horses with superficial digital flexor tendinitis to the previous level of activity without relapse.[7]

Although the mean value of 494,5 fibroblasts per mm^2 in the ESWT test group did not differ significantly from 789,5 per mm^2 in control group, the treatment's value was close to 459 fibroblasts per mm^2 proposed as normal for horse tendons by authors.[1,7] These data allowed us to speculate that the lower number of fibroblast detected in the test group (G1) may represent a later remodeling phase in the repair process.

The small amount of residual neoformed vessels and mononuclear infiltrate observed in the group

Table I. Mean values of ecogenicity in the lesion area, percentage of the lesion area and parallelism score, observed in the experimental groups through ultrasonography examination on days 7, 30, 60, 90 and 120 of the experiment.

	7th	30th	60th	90th	120th
Ecogenicity					
G1*	3^{Aa**}	$2,5^{Aa}$	2^{ABa}	$1,5^{Ba}$	1^{Ba}
G2	3^{Aa}	2^{Aa}	3^{Aa}	2^{Aa}	1^{Ba}
Percentage of the lesion area					
G1	28.02^{Aa**}	18.68^{Ba}	12.45^{Ca}	6.42^{Da}	3.02^{Da}
G2	32.70^{Aa}	24.00^{Ba}	11.37^{Ca}	9.53^{Ca}	6.85^{Da}
Collagen fibers parallelism					
G1	0^{Aa**}	1^{Aa}	0^{Aa}	$1,5^{Ba}$	3^{Cc}
G2	0^{Aa}	0^{Aa}	0^{Aa}	1^{Aa}	1^{Aa}

*G1 = test group; G2 = control group.
For each group, medians followed by capital letters did not differ significantly (p>0.05). For each phase, medians followed by small letters did not differ significantly (p>0.05).
The results obtained in the histopatological examination performed on the 120 th day after the lesion, showed fibroplasia, as also reported in literature.[1] We observed differences between groups in terms of degree of collagen fiber maturation based on the identification of a low number of fibroblasts per unit area with elongated nuclei, few residual neoformed vessels, a few traces of mononuclear inflammatory infiltrate and a parallel arrangement of collagen fibers in test group, observed under the microscope (**Table 2**).

submitted to ESWT (G1) indicated a higher speed of maturation of the repair process compared with control (G2). Similar data were reported by Willians 9 who stated that the reduction of cellularity and vascularization suggests progressive maturation of granulation tissue.

The present results demonstrate that the parallel arrangement of collagen fibers in the ESWT test group (G1) was more evident than in control group (G2) (**table 2**). When comparing these results with those reported by Alves et al.[7] and Goodship and Birch,[1,11] it can be observed that during the process of tendon repair, collagen fibrils are irregularly deposited, with predominant longitudinal alignment as the process matures. In our study the process of collagen fiber remodeling was more efficient in test group than in the control one.

The fact that ESWT had stimulated the alignment of collagen fibers during the course of the repair process, led us to believe that the ESWT in the present experiment had a high beneficial effect on the quality of tendon repair.[1,11,12] Alves et al.[7] emphasized the importance of the high degree of parallelism of collagen fibers, demonstrating the correlation between this characteristic and the increased resistance of tendon fibers.

We concluded that the effect of ESWT on tendon lesions allowed for a significant improvement in the quality of the tendon repair and favorable prognosis for the horse principally due to the arrangement of the collagen fibers.

The next phase of a future study could be the investigation of the proportion of the two types of collagen fibers (I and II) in this repair tissue and the mechanical properties of the scar.

[a] Collagenase type I, Sigma, USA
[b] Sedivet, Boehringer Ingelheim, Brasil
[c] Lidocaína 2%, Cristália, Brasil
[d] SSD 900, Aloka, Japan
[e] Versatron, HMT, Swiss
[f] Sedazine, Fort Dodge, Brasil
[g] Vetanarcol, Konig, Brasil
[h] Valium, Roche, Brasil
[i] EGG, Henrifarma, Brasil

Table 2. Mean values of number of fibroblast cells in the lesion area and of parallelism score, observed in the experimental groups through histopathological examination on the 120th day of the experiment.

	G1	G2
Mean fibroblast number	494.5[a*]	789.5[a]
Median parallelism score	3[a]	1[b]

*G1 = test group; G2 = control group.
For each group, medians followed by lower case letters were did not differ significantly (p>0.05).

References

1. Goodship AE, Birch HL, Wilson AM. The pathobiology and repair of tendon and ligament injury. Vet Clin North Am Equine Pract. 1994;10(2):323-349.
2. Dyson S. Proximal suspensory tendinitis in the forelimb and the hindlimb. In: Proceedings. Am Assoc Equine Pract. 2000;46:127-142.
3. McClure SR, Evans RB. In vivo evaluation of extracorporeal shock wave therapy for collagenase induced suspensory ligament tendinitis. In: Proceedings. Am Assoc Equine Pract. 2002;48:378-380.
4. Boening KJ, Löffeld S, Weitkamp K, Matuschek S. Radial extracorporeal shock wave therapy for chronic insertion desmopathy of the proximal suspensory ligament. In: Proceedings. Am Assoc Equine Pract. 2000;46:203-207.
5. Wang CJ, Paich, Avery SY. Shock waves enhanced neovascularization. at the tendon bone junction. An experimental dog model, In proceedings. 3rd Congress Of The International Society For Musculoskeletal Shock Wave Therapy, 2000; 96.
6. Caminoto EH, Alves ALG, Amorim RL, Thomassian A, Hussni CA, Nicoletti JL. Ultrastructural and immunocytochemical evaluation of the effects of extracorporeal shock wave treatment in the hind limbs of horses with experimentally induced suspensory ligament desmitis. Am J Vet Res. 2005; 66 (5):892-896.
7. Alves ALG, Rodrigues MAM, Aguiar AJA, Thomassian A, Nicoletti JLM, Hussni CA, Borges AS. Effects of beta- aminopropionitrile fumarate and exercise on equine tendon healing: Gross and histological aspects. J Equine Vet Sci. 2001; 21(7):335-340.
8. Foland JW, Trotter GW, Powers BE, Wrigley RH, Smith FW. Effect of sodium hyaluronate in collagenase-induced superficial digital flexor tendinitis in horses. Am J Vet Res. 1992; 53(12):2371-2376.
9. Williams IF, McCullagh KG, Goodship GD, Silver IA. Studies on the pathogenesis of equine tendonitis following collagenase injury. Res Vet Sci. 1984; 36:326-338.
10. McClure SR, VanSickle D, Evans R, Reinertson EL, Moran L. The effects of extracorporeal shock-wave therapy on the ultrasonographic appearance of collagenase-induced equine forelimb suspensory ligament desmitis. Ultrasound in Med & Biol. 2004; 30(4): 461-467.
11. Crowe O, Dyson SJ, Wright IM, Schramme MC, Smith RKW. Treatment of 45 cases of chronic hindlimb proximal suspensory desmitis by radial extracorporeal shockwave therapy. In: Proceedings. Am Assoc Equine Pract. 2002;48:322-325.
12. Kersh KD, McClure S, Evans RB, Moran L. Ultrasonographic evaluation of estracorporeal shock wave therapy on collagenase-induced superficial digital flexor tendonitis. In: Proceedings. Am Assoc Equine Pract. 2004;50:257-260.

Instructions for Authors

Newsletter of Extracorporeal Shockwave Therapy is an international, peer-reviewed journal produced by International Society for Musculoskeletal Shockwave Therapy(ISMST) and is issued three times a year.

Newsletter of Extracorporeal Shockwave Therapy offers the opportunity to publish original research, clinical studies, review articles, case reports, clinical lessons, abstracts, book reviews, conference reports and communications regarding the scientific or medical aspects shockwave therapy.

Manuscript Submission

All manuscripts should be sent to the Editor:

By e-mail: prds@uol.com.br
On disk and mail to:
Dr Paulo Roberto Dias dos Santos
Rua Nathanael Tito Salmon, 233
Osasco - São Paulo - Brazil
CEP 06016-075

We encourage authors to submit manuscripts via e-mail. When submitting by e-mail, print mail address and telephone and fax numbers also should be included.

Manuscript Categories

All articles should be well-written in plain English, whereby jargon, acronyms, abbreviations and complicated data should be avoided.

Scientific research:

Theoretical or experimental (basic or applied) scientific research or the practical application of this research. The article should consist of an abstract, key words, introduction, methods, results, discussion, and conclusion.

Length: The manuscript should be no longer than 2,500 words, including title page, abstract, references, legends and tables.

Review articles:

Review articles on topics of general interest are welcomed. Reviews should include the specific question or issue that is addressed and its importance for the shockwave therapy community, and provide an evidence-based, balanced review on this topic. The article should include a description of how the relevant evidence was identified, assessed for quality, and selected for inclusion; synthesis of the available evidence such that the best-quality evidence should receive the greatest emphasis; and discussion of controversial aspects and unresolved issues. Meta-analyses also will be considered as reviews. Authors interested in submitting a review manuscript should contact the editorial office prior to manuscript preparation and submission.

Length: Approximately 2,000 to 2,500 words and no more than 40 references.

Case reports

Authors are encouraged to submit articles with interesting case reports with relevant information regarding diagnosis and therapy, unique for shockwave therapy. The articles should be short, accurate and easy to understand, and should consist of the following:

- A summary with the clinical relevance;
- An introduction explaining the clinical problem;
- A short report of the cases, consisting of history, physical examination, further investigation, treatment and follow-up.
- A discussion, whereby the clinical consequences are described and the most interesting aspects of the case report.

Length: Approximately 750 to 1,200 words and a maximum of 15 references.

Clinical lesson

Authors are invited to give a description and background information of developments in the field of further diagnostics and clinical tests and methods that are relevant to all aspects of shockwave therapy, training and rehabilitation. It is not necessary to include examples of patients, as in case reports. The articles should be up-to-date, short, accurate, and easy to understand and should contain the following:

- A summary with the clinical relevance (max. 150 words)
- And introduction with the theme of the article
- A description of the used test method or diagnostic
- A conclusion with the practical relevance and practical tips.

Length: Approximately 750 to 1,200 words and a maximum of 5 references.

National organisation communications

National organisations are invited to describe any aspect of medical care or science in their country, e.g. the function of their medical committee, medical care of their players, research that is being conducted etc.

Approximately 300 to 500 words

Letters to the editor:

Letters discussing an article that has been published in Journal of Extracorporeal Shockwave Therapy have the greatest chance of acceptance if they are sent in with 2 months of publication. Letters that are approved will be forwarded to the author, who will have 6 weeks to respond. The original letter and the reply will be published simultaneously.

Length: Such letters should not exceed 400 words of text and 5 references. Research Letters reporting original research also are welcome and should not exceed 600 words of text and 6 references and may include a table or figure.

Review of the Literature

Authors are invited to submit summaries of published article of particular interest for the shockwave therapy community. The opinion of the author should be stated following each summary.

Length: Such a review should be approximately 500 to 700 words. A review of three articles simultaneously should be no longer than 1,000 words.

Conference reports and Abstracts

Authors are invited to submit reports of conferences they have attended, and to include one to three photographs taken at the meetings. Please include the names and highest titles of the persons that can be identified in the photographs. Summaries of work presented at the conference may be submitted for publication as well.

Length: 300 to 500 words per report or abstract.

Manuscript Preparation

Manuscripts should be prepared in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Vancouver Style). http://www.nlm.nih.gov/bsd/uniform_requirements.html

- If submitting by e-mail, text, tables, and figures should be included in the same file. Do not submit duplicate copies by mail or fax.
- Articles should be in Microsoft Word format.
- Double-space throughout, including title page, abstract, text, acknowledgements, references, figure legends, and tables.
- Do not use abbreviations in the title or abstract and limit their use in the text.
- Please use Times New Roman, size 12.
- On the title page include the full names, highest academic degrees, and affiliations of all authors. If an author's affiliation has changed since the work was done, list the new affiliation as well.
- Figures, summary tables and diagrams should be numbered consecutively throughout the paper. Photographs should be clearly labelled.
- References. Number references in the order they appear in the text; do not alphabetise. In text, tables, and legends, identify references with superscript Arabic numerals. When listing references, follow AMA style and abbreviate names of journals according to Index Medicus. List all authors and/or editors up to 6; if more than 6, list the first 3 followed by et al.

– Journal: Kibler WB. The role of the scapula in athletic shoulder function. Am J Sports Med. 1998;26(2):325-337.

– Book: Perry J. Biomechanics of the shoulder. In: Rowe CR, ed. The shoulder. London: Churchill Livingstone, 1988:1-15.

- Footnotes should be avoided.

Review process

Contributions will be reviewed by the editorial board for scientific research, review papers, case reports, clinical lessons, and abstracts. Manuscripts should meet the following criteria: material is original; writing is clear; study methods are appropriate; the data are valid; conclusions are reasonable and supported by the data; information is important; and topic has general shockwave therapy interest.

Manuscripts with insufficient priority or quality for publication are rejected promptly. Other manuscripts are sent to expert consultants for peer review. Peer reviewer identities are kept confidential, but author identities are known by reviewers. The existence of a manuscript under review is not revealed to anyone other than peer reviewers and editorial staff.

Intellectual property

- The article must be your own original work.
- If the article contains any photographs, figures, diagrams, summary tables, graphs or other non-textual elements that are not your own original work, you must ensure that you have obtained written permission from the copyright owner to include their work in your article for publication in Journal of Extracorporeal Shockwave Therapy. Permission letters must be submitted with your article.

DUPLO PODER

ARCOXIA* (ETORICOXIBE), MSD

PODER rápido e prolongado

Início da analgesia já aos 24 MINUTOS

Em um estudo clínico de odontalgia aguda com ARCOXIA 120 mg:[1+]

24 minutos, início da ação[1]

X

24 horas, duração da ação[1]

O efeito analgésico persistiu por até 24 HORAS

Novas embalagens

1 x/dia

[+] ARCOXIA 120 mg só deve ser utilizado durante o período sintomático agudo.

Referência bibliográfica: 1. Malmstrom K, Sapre A, Coughlin H et al. Etoricoxib in acute pain associated with dental surgery: A randomized, double-blind, placebo- and active comparator-controlled dose-ranging study. *Clin Ther* 2004;26(5):667-679.

Resumo do estudo: estudo com distribuição randômica, de grupos paralelos, que envolveu 398 pacientes com dor moderada a intensa após extração de, pelo menos, dois terceiros molares. Os pacientes receberam uma dose única de 60 mg, 120 mg, 180 mg ou 240 mg de ARCOXIA, 400 mg de ibuprofeno e placebo. Os pacientes interromperam dois cronômetros durante o tratamento: quando alcançavam alívio perceptível da dor e quando alcançavam alívio significativo da dor. A intensidade e o alívio da dor foram medidos já 15 minutos após a administração da dose. O início da analgesia ocorreu já 24 minutos após a dose em pelo menos 50% dos pacientes tratados com 120 mg de ARCOXIA e a analgesia persistiu por até 24 horas após a dose em 72% dos pacientes tratados com essa dose; as doses mais altas de ARCOXIA não proporcionaram nenhum efeito clínico adicional.

ARCOXIA (etoricoxibe), MSD. INDICAÇÕES: tratamento agudo e crônico dos sinais e sintomas da osteoartrite e da artrite reumatóide, da gota aguda e da dismenorréia primária; alívio da dor aguda e crônica. **CONTRA-INDICAÇÃO:** hipersensibilidade a qualquer componente do produto. **PRECAUÇÕES:** ARCOXIA não é recomendado para pacientes com doença renal avançada; se o tratamento for necessário, recomenda-se monitorização rigorosa da função renal desses pacientes. Deve-se ter cautela ao iniciar o tratamento com ARCOXIA em pacientes com desidratação considerável e considerar a possibilidade de retenção hídrica, edema ou hipertensão quando ARCOXIA for utilizado em pacientes com edema, hipertensão ou insuficiência cardíaca preexistentes. Os médicos devem estar cientes de que determinados pacientes podem desenvolver úlcera(s) no trato gastrintestinal superior, independentemente do tratamento, especialmente naqueles com mais de 65 anos de idade. Foram relatados aumentos de ALT e/ou AST em cerca de 1% dos pacientes tratados durante mais de um ano em estudos clínicos; essas alterações desapareceram em seguida e, em cerca de metade dos casos, sem interrupção do tratamento. Em caso de disfunção hepática persistente, ARCOXIA deve ser descontinuado. ARCOXIA deve ser utilizado com cautela por pacientes que já tenham apresentado crises agudas de asma, urticária ou rinite causadas pelo uso de salicilatos ou inibidores não específicos da ciclooxigenase. ARCOXIA pode mascarar a febre, que constitui um sinal de infecção. ARCOXIA só deve ser usado durante os dois primeiros trimestres da gravidez se o benefício potencial justificar o possível risco para o feto. Não se sabe se ARCOXIA é excretado no leite humano; por isso, quando ARCOXIA for administrado a nutrizes deve-se considerar a importância do medicamento para a mãe ao se decidir entre descontinuar a amamentação ou a medicação. A segurança e a eficácia em pacientes pediátricos não foram estabelecidas e, em geral, não foram observadas diferenças no perfil de segurança e na eficácia do medicamento entre pacientes idosos (65 anos de idade ou mais) e pacientes mais jovens. **INTERAÇÕES MEDICAMENTOSAS:** *Tratamento crônico com varfarina:* a administração de 120 mg de ARCOXIA uma vez ao dia foi associada com aumento no tempo de protrombina de aproximadamente 13% (*International Normalized Ratio* - INR). *Rifampicina:* ocorreu redução de cerca de 65% das concentrações plasmáticas do etoricoxibe quando este foi administrado com a rifampicina. *Metotrexato:* doses de 60 mg e 90 mg ao dia de ARCOXIA durante 7 dias não exerceram efeito na concentração plasmática ou na depuração renal de 7,5 mg a 20 mg de metotrexato em doses únicas semanais para o tratamento da artrite reumatóide. Em um estudo, a dose de 120 mg de ARCOXIA aumentou a concentração plasmática do metotrexato em 28% e reduziu a depuração renal do metotrexato em 13%; por isso, deve-se monitorar a toxicidade relacionada ao metotrexato quando forem administradas doses maiores que 90 mg de ARCOXIA ao dia com essa medicação. *Inibidores da ECA:* relatos sugerem que pode haver diminuição dos efeitos anti-hipertensivos dos inibidores da ECA quando ARCOXIA for administrado com essas medicações. *Lítio:* relatos sugerem que pode haver aumento dos níveis plasmáticos de lítio quando ARCOXIA for administrado com lítio. *Ácido acetilsalicílico em baixas doses:* pode ser utilizado concomitantemente a ARCOXIA; este, porém não exerce efeitos sobre as plaquetas e não substitui o ácido acetilsalicílico para profilaxia cardiovascular. **REAÇÕES ADVERSAS:** as seguintes experiências adversas relacionadas à medicação foram relatadas (incidência ≥1%) em estudos clínicos de 12 semanas sobre osteoartrite, artrite reumatóide ou dor lombar crônica: astenia/fadiga, tontura, edema de membros inferiores, hipertensão, dispepsia, pirose, náuseas, cefaléia e aumento de ALT e AST. O perfil de experiências adversas relatadas nos estudos sobre gota aguda e analgesia aguda foi similar ao relatado nos estudos combinados de osteoartrite, artrite reumatóide e dor lombar crônica. **POSOLOGIA:** *Osteoartrite:* 60 mg uma vez ao dia. *Artrite Reumatóide:* 90 mg uma vez ao dia. *Gota Aguda:* 120 mg uma vez ao dia (somente durante o período sintomático agudo). *Dor Aguda e Dismenorréia Primária:* 120 mg uma vez ao dia (somente durante o período sintomático agudo). *Dor Crônica:* 60 mg uma vez ao dia. (Doses maiores que as recomendadas para cada indicação ou não apresentaram eficácia adicional ou não foram estudadas; portanto, as doses acima são as doses máximas recomendadas.) *Insuficiência Hepática:* em pacientes com insuficiência hepática leve (escore de Child-Pugh 5-6), a dose de 60 mg uma vez ao dia não deve ser excedida. Em pacientes com insuficiência hepática moderada (escore de Child-Pugh 7-9), a dose de 60 mg em dias alternados não deve ser excedida. Não há dados clínicos ou farmacocinéticos em pacientes com insuficiência hepática grave (escore de Child-Pugh >9). *Insuficiência Renal:* o tratamento com ARCOXIA não é recomendado para pacientes com doença renal avançada (*clearance* de creatinina <30 ml/min). Não há necessidade de ajuste posológico para pacientes com insuficiência renal leve/moderada (*clearance* de creatinina ≥30 ml/min). **REGISTRO MS:** 1.0029.0035. VENDA SOB PRESCRIÇÃO MÉDICA.

Nota: antes de prescrever ARCOXIA, recomendamos a leitura da Circular aos Médicos (bula) completa para informações detalhadas sobre o produto.

MERCK SHARP & DOHME

MC 040/05 03-2006-ACX-05-BR-040-J

www.msdonline.com.br

MERCK SHARP & DOHME on line
0800-122232
E-mail: online@merck.com
www.msdonline.com.br