



Technical Note

Prevention of arthrofibrosis during knee repair by extracorporeal shock wave therapy: Preliminary study in rabbits

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ABSTRACT

Introduction: Surgery or trauma may induce extensive arthrofibrosis around joints and tendon for the restrictive range of motion. Although some approaches were proposed, this problem is not solved satisfactorily. Extracorporeal shock wave therapy (ESWT) has been used for orthopedic, musculoskeletal, and fibrotic disorders. Whether it could prevent the formation of arthrofibrosis during the joint repair is unknown.

Methods: Intra-articular adhesions were created in the right knee of the rabbit by cortical bone shaving and subsequent cast immobilization. Arthrofibrosis in the control and ESWT group was evaluated and compared at week 4.

Results: Macroscopic score of arthrofibrosis and contracture angle of the control group are significantly higher. Histologically, the apparent gap between patella and tibia, loose connective tissue, and much less density of the blood vessel are found in the ESWT group.

Conclusions: ESWT could noninvasively, effectively, and safely prevent the formation of arthrofibrosis during the knee repair.

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Introduction

Arthrofibrosis is the abnormal hyperplasia of fibrous tissue in a joint (e.g., elbow, shoulder, knee, and ankle) with an unclear etiopathogenesis that stretches across the articular capsule of the joint and binds the joint surfaces after the trauma or surgery [1]. The development of arthrofibrosis is initiated by an inflammatory response with neutrophil infiltration into the clot that forms around the injured site, the migration of macrophages, and then the emergence of fibroblast with subsequent collagen deposition [2,3]. Subsequently, widespread fibrous tissue growth and adhesion tissue matures into scar-bands, inhibits joint biomechanics, leads to stiffness and abnormal joint contact pressures, and predisposes the joint to cartilage generation. As a result, the range of motion (ROM) of a joint is decreased significantly after removing the plaster fixture [4–6]. Arthrofibrosis of the knee leads to loss of motion, pain, muscle weakness, swelling, and functional limitation. Scar tissue may persist for months or years, and slight knee stiffness may persist and become more apparent after routine

rehabilitation and joint motion exercises, which is more severe after high-energy, multi-ligament injury than after single-ligament, low-energy injury. Attempts to regain normal function of an arthrofibrotic joint may lead to further tissue injury, resulting in swelling and additional discomfort. The incidence of knee arthrofibrosis is between 4% and 35% depending on the types, causes, and severity of injury (i.e., anterior cruciate ligament reconstruction, primary total knee arthroplasty, elective intra-articular surgeries) [2,7,8].

All available solutions for arthrofibrosis could be categorized as prevention and operation. Biologic and synthetic materials, such as vessel grafts, fascial patch grafts, polyethylene, and silastic sheeting, were studied as barriers against adhesion. The early accelerated rehabilitation program and exercises help prevent the development of contractures and initiate the immediate knee ROM without risk of graft injury. Numerous biochemical agents were also examined to suppress the actions of adhesion formation, including steroids, intravenous corticosteroids, oral nonsteroidal anti-inflammatory agents, hyaluronic acid, and transforming growth factor-beta (TGF- β) [9]. The use of a compression dressing, physical therapy, hydrodilatation, electric fields, and cryotherapy may limit swelling and inflammation and subsequently, reduce the odds of experiencing arthrofibrosis. Once arthrofibrosis is diagnosed, a course of physical therapy is often recommended to regain

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ROM through gentle manipulation. Manipulation under anesthesia (MUA) is proposed as a first-line treatment for arthrofibrosis (i.e., within 4–12 weeks of anterior cruciate ligament reconstruction for flexion of $<90^\circ$), involving indiscriminate tearing of connective tissues that can take place in tissue planes different from the original planes despite the use of physical therapy. Overaggressive or significantly delayed manipulation should be avoided to prevent complications, such as chondral damage, distal fem or patella fracture, patellar tendon rupture, stimulation of myositis ossificans of the quadriceps, and ossification of the medial collateral ligament. Minimally invasive arthroscopic lysis of adhesions performed on an outpatient basis has been approved safe and effective in breaking up the arthrofibrosis and scar tissue in the joint. Only when nonoperative and arthroscopic techniques are unsuccessful at restoring knee ROM, open debridement is recommended to extensively release the involved capsule and resect all fibrous tissue as a salvage procedure. However, injudicious surgical release or removal may stimulate more fibrous tissue formation and worsen the condition. After the initial treatment, numerous rehabilitation activities are necessary to maintain motion and prevent the recurrence, which is painful, taxing, and long (up to 2 years), so that adequate pain control is critical in the postoperative period to maintain the gains obtained in surgery. Increased recognition of this problem in the past two decades has led to better prevention and improved management of these injuries [2]. However, failures to obtain symptomatic improvement and the presence of continued functional disability after joint ligament injury raise the need for the innovative and effective solution.

Shock waves have been applied to fragment kidney stone noninvasively since the 1980s with great success in urology. Immediately after the invention of the lithotripter, extracorporeal shock wave therapy (ESWT) was applied for nonunions and delayed unions as well as certain musculoskeletal disorders, such as plantar fasciitis, plantar heel pain, chronic Achilles tendinopathy, lateral epicondylitis or tennis elbow, calcific and noncalcific tendonitis of the rotator cuff [10–13]. It can stimulate soft-tissue healing, and induce neovascularization, particular elaboration of callus, enzyme release as a convenient and cost-effective therapeutic modality without the surgical risks and pain. Furthermore, ESWT has also been introduced in the treatment of patients with fibrotic conditions, such as adhesive capsulitis, plantar fibromatosis (Ledderhose's disease), penile fibromatosis (Peyronie's disease), capsular contracture, and Dupuytren contracture [14–16]. It improves short-term functionalities of shoulder adhesive capsulitis, such as the activities-of-daily living parameter, pains, and ROM, with transient and tolerable side effects [17,18]. No serious adverse events such as infection or hyperesthesia were reported. The advantage of high-energy ESWT is that it is widely applicable in out-of-hospital settings and is relatively inexpensive without any long-term complications [19]. However, all of these studies are on the joint contracture after the occurrence of fibrotic adhesion. Preventing the formation of arthrofibrosis during the joint repair is much more preferred.

We hypothesized that because of the reduction of ROM on the adhesive capsulitis ESWT may also be able to prevent the abnormal hyperplasia of fibrous tissue in the artificially damaged knee joints during the immobilization. Thus, the objective of this study was to explore the possibility of high energy ESWT on the arthrofibrosis formation immediately after the knee surgery in an animal model using the established protocol, investigate the effect of ESWT, such as the contracture angle, macroscopic observation, and histological examination, and compare the outcomes in the ESWT group with those in the control group.

Materials and methods

Experimental protocol

This study was approved by the Institutional Review Board and performed under the guidelines and care of animals in research, and its protocol is shown as Fig. 1. Female New Zealand white rabbits aged 3–4 months in the weight of 2.5–3.0 kg were used as the animal model. A total of 12 rabbits were randomly assigned to control and ESWT with the equal number ($n=6$) in each group. The sample size was determined using power analysis (G*Power, Universität Kiel, Germany) to avoid both type 1 and 2 errors. General anesthesia of rabbit was performed by intramuscular (i. m.) administration of xylazine hydrochloride (10 mg/kg) and ketamine hydrochloride (50 mg/kg). Baytril and carprofen were given i.m. pre-operation. Animals were maintained with 1.5–3% isoflurane during the surgical procedure. The established protocol was used to introduce knee arthrofibrosis [9]. Incision sites were shaved and swabbed with 1% cetrimide followed by 1% povidone-iodine alcohol. The right knee joint of the rabbit was opened through a medial parapatellar approach, and the medial and lateral sides of the femoral condyle were exposed. With the use of a template, a square of the cortical bone in the size of 5×10 mm was removed with a water-cooled dental burr to a depth of 3 mm [9]. The burr had a head diameter of 1.0 mm and was equipped with a regulator to control the depth of shaving. The cortical bone was 0.4–0.7 mm thick in these portions, and cancellous bone was exposed at the bottom of the squares. Incision site was closed with vicryl 4/0 for subcutaneous tissue, and monocryl 5/0 for subcuticular. All surgery was performed with appropriate care during the whole procedure. Immediately following the surgery, the knee joint of the animals was immobilized in the fully flexed position with a fiberglass cast from the groin to the foot. On the cast, a circular opening in a diameter of 1.5 cm was made (before the cast hardens) to facilitate administration of ESWT. Cotton pads were added under the cast to prevent pressure ulcers. The contralateral left knee was untreated (Fig. 2).

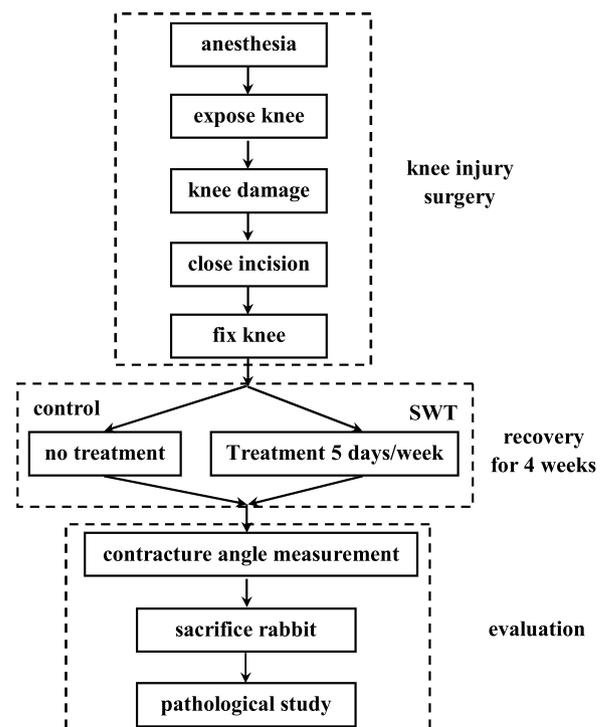


Fig. 1. Protocol and flowchart of the animal experiment.

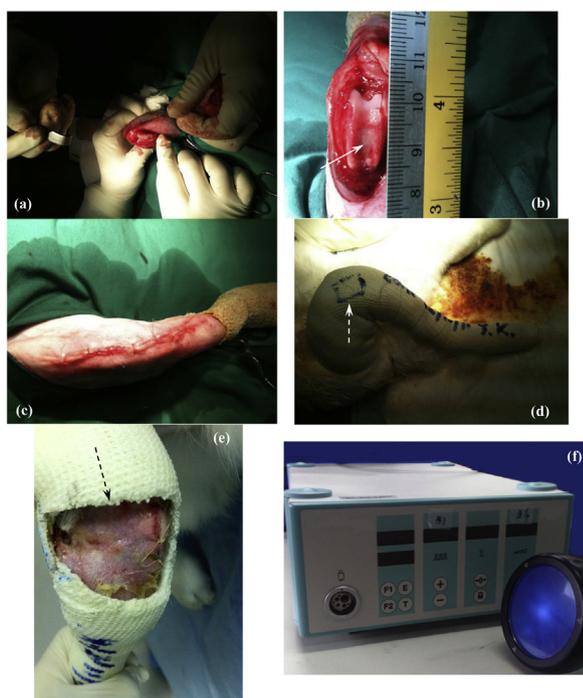


Fig. 2. Representative photo of (a) exposing the knee, (b) causing the damage to the knee (white arrow), (c) closing the incision, (d) fixing the knee, (e) opening on the cast (dashed arrow), and (f) the shock wave therapy device.

Extracorporeal shock wave therapy

In the ESWT group, 1000 shock waves (Piezason 100 plus, Richard Wolf GmbH, Knittlingen, Germany) at energy flux density of 0.2 mJ/mm² that is considered as high energy [19] were delivered at the pulse repetition frequency of 3 Hz (about 5.5 min. for each session), 5 days per week for 4 weeks. Gel pad with the penetration depth of 5 mm was attached to the aperture of the transducer, and the opening in the cast was filled with ultrasound coupling gel (Aquasonic 100, Parker Laboratories, Fairfield, NJ) for the propagation of shock waves. The first therapeutic procedure was done immediately after the cast immobilization when the animals were still under anesthesia. The transducer was applied to the opening of the knee cast. On the subsequent days, the rabbit was physically restrained in a rabbit restrainer cage. In the control group, the animals were left untreated for 4 weeks. All rabbits were housed individually in cages and fed with standard diet and drinking water ad libitum. General health status of the animal, incision site, swelling or edema in the foot of the cast knee, and lower extremity ischemic gangrene were monitored daily post-operation.

Measurement of the contracture angle

Four weeks after the surgery, the casts were gently removed, and the contracture angle of the right knee was measured [9]. The rabbit was laid on its left side on the radiographic table while it remained deeply anesthetized. A looped steel wire (1.0 mm in diameter) was hooked on the lower leg 10 cm distal from the proximal joint surface of the tibia. A tension was produced by a 500-g weight (4.9 N) attached to the other end of the wire and was given perpendicularly to the tibial axis, which was enabled by sliding the pulley on the rail. The knee was extended by pulling the wire with this tension while the right thigh was firmly fixed to the table. Thus, extension torque of 0.49 Nm was applied to the joint. The radiographs were taken after 5 min of the equilibration interval using an x-ray unit (Universal VetTek 400, UMG/DEL Medical, Harrison, NY) with its tube

positioned exactly above the knee joint. The increment of the flexion angle of the right knee joint of each rabbit was determined on a pair of radiographs taken immediately after cast removal and defined as the contracture angle [9]. The contracture angle was the main outcome measure in this study.

Macroscopic evaluation

Then all animals were euthanized by intravenous administration of an overdose of pentobarbital sodium (100 mg/kg). The right knee was held at 90° of flexion, and the joint was opened through a parapatellar lateral approach. With the use of loupe magnification, adhesions between the lateral femoral condyle and the joint capsule were evaluated by a blinded observer using a severity score of 0–4: grade 0 for no adhesions; grade 1 for filmy, weak adhesions; grade 2 for mild adhesions; grade 3 for moderately dense adhesions; and grade 4 for dense, fibrous adhesions [20].

Histological examination

Immediately after the macroscopic evaluation, the right knee joints were excised with the surrounding soft tissue, fixed in 10% neutral buffered formalin for 1 week, and decalcified in 10% (w/vol) disodium EDTA in phosphate buffered saline solution (pH 7.4) at 4 °C for 4 weeks. The samples were embedded in paraffin, and 6- μ m transverse sections parallel to the femoral axis were excised from the condylar portion of the femur, including decorticated areas on both sides. The sections were mounted on silane-coated slides and stained by Gomori's one-step method. Arthrofibrosis in the lateral femoral condyles were evaluated under a light microscope (CKX-41, Olympus, Tokyo, Japan). Vascular density and vascular length density in the histological slices were quantitatively determined using the established plugins in the ImageJ (National Institute of Health, Bethesda, MD). Vascular density is defined as the percentage of vessel area over the total area while vascular length density as that of skeletonized vessel area over the total area. Both the macroscopic evaluation and histological examination are the secondary outcome measures.

Statistical analysis

To determine the statistical difference between the test groups, one-way analysis of variance (*t*-tests were performed in SigmaPlot (Systat Software, San Jose, CA). The level of statistical significance was fixed at $p < 0.05$. Data are presented as an average value \pm standard deviation.

Results

During the experiment, no rabbits showed severe or chronic distress that cannot be relieved with therapeutic intervention and no pressure ulcers from the casts for the infection and necrosis, which shows the tolerance and safety of ESWT. Representative radiographs of the angle of rabbit knee in the control and ESWT groups before and after the contracture are shown in Fig. 3. Contracture angles are $60^\circ \pm 4.5^\circ$ and $7.5^\circ \pm 9.3^\circ$ in the control and ESWT groups, respectively, with the significant difference between them ($p < 0.05$ in Fig. 4). The control group was categorized as type 4 arthrofibrosis, flexion loss of more than 30 degrees, referred to the grading system [21].

Macroscopically, dense fibrous adhesions were observed around the decorticated areas of the rabbits in the control group, but little arthrofibrosis was developed in the ESWT group. Scores for adhesions of these two groups are significantly different (3.83 ± 0.75 vs. 1.17 ± 0.41 , $p < 0.05$ in Table 1). In the histological slices, a clear gap between the patella and tibia is found in the

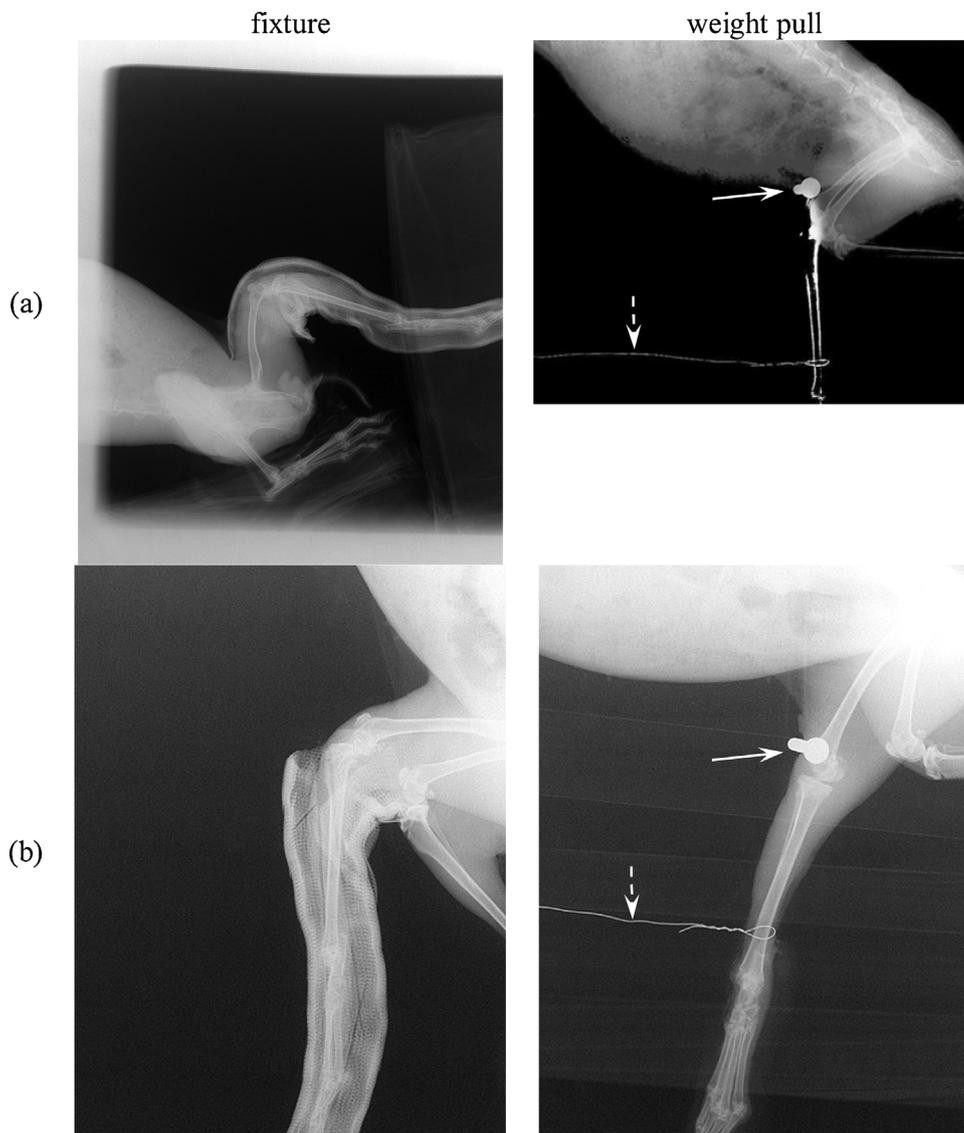


Fig. 3. Representative X-ray photos of rabbit's leg in the (a) control and (b) shock wave treatment group at the fixture and after the weight pull. Comparison of the motion degree of knees of (left) control and (right) shock wave treated one after immobilizing the right knee of the New Zealand white rabbit. Arrow: pivot to firmly fixing the right thigh to the table, dashed arrow: pulling steel wire.

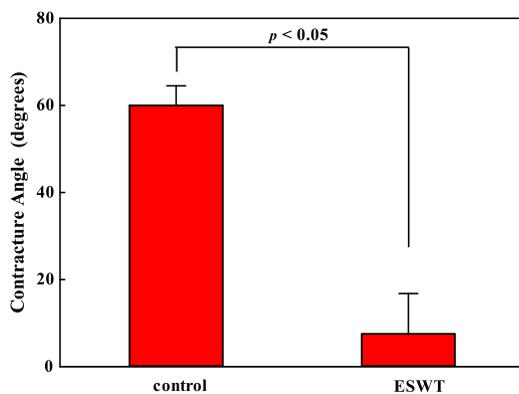


Fig. 4. Comparison of the contracture angle of rabbit knee in the control and extracorporeal shock wave treatment (ESWT) group in *in vivo* experiment ($n=6$).

rabbit knee by ESWT (see Fig. 5). Dense fibrous adhesions and newly formed bones with a thin layer of the covering fibrous tissue were observed around and at the bottom of the decorticated areas in the knee, respectively. Immature fibroblast was the major cell type in the arthrofibrosis. The density of blood vessels (shown by the arrows) in the control group is much higher than that of the ESWT group, and the fibrosis in the ESWT group is mostly loose connective tissues. Vascular density and vascular length density in the histological slices in the control group ($18.04 \pm 2.53\%$ and $1.88 \pm 0.27\%$) and the ESWT group ($14.26 \pm 1.92\%$ and $1.47 \pm 0.21\%$) are shown in Fig. 6 with statistical differences ($p < 0.05$).

Discussion

We performed the first animal experiment of ESWT on the prevention of arthrofibrosis during the knee healing. The significantly lower contracture angle, fibrous tissue adhesion between the patella and tibia, and the densities of the fibrous cell

Table 1
Comparison of animal experiment results.

control						
rabbit	age (weeks)	weight (kg)	adhesion score	contracture angle (°)	vascular density (%)	vascular length density (%)
#1	27	2.85	4	63.3	15.64	2.13
#3	28	2.98	4	56.5	18.51	1.51
#4	28	2.97	3	66.2	19.87	1.80
#6	26	2.65	3	57.5	15.02	1.94
#10	27	2.73	4	62.2	21.69	2.22
#11	25	2.61	5	54.5	17.48	1.68
	26.8 ± 1.2	2.80 ± 0.16	3.83 ± 0.75	60.03 ± 4.54	18.04 ± 2.53	1.88 ± 0.27
ESWT: 1000 shots, P _{II} of 0.2 mJ/mm ² , PRF of 3 Hz, 5 days/week for 4 weeks						
#2	27	2.90	1	2.7	16.33	1.53
#5	26	2.84	1	5.4	12.99	1.37
#7	28	2.96	1	4.5	16.02	1.19
#8	28	2.92	2	3.7	11.64	1.81
#9	27	2.87	1	2.2	13.18	1.54
#12	26	2.75	1	26.3	15.41	1.35
	27 ± 0.9	2.87 ± 0.07	1.17 ± 0.41	7.47 ± 9.30	14.26 ± 1.92	1.47 ± 0.21
statistical comparison						
p value	0.77	0.25	0.001	0.0002	0.03	0.009

P_{II}: energy flux density of shock wave, PRF: pulse repetition frequency.

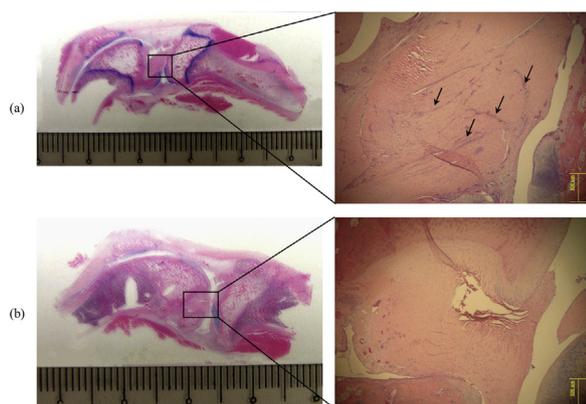


Fig. 5. Representative histological slices of rabbit's knee in the (a) control and (b) ESWT group, respectively. Arrows show the blood vessels.

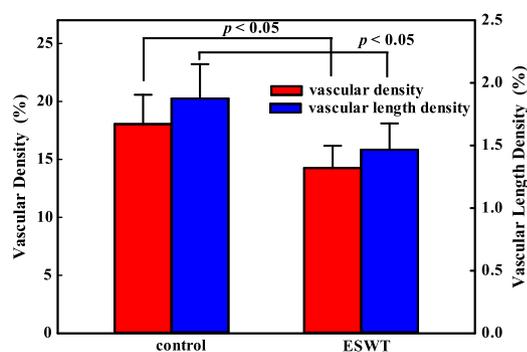


Fig. 6. Comparison of the vascular density and vascular length density of rabbit knee in the control and extracorporeal shock wave treatment (ESWT) group in *in vivo* experiment ($n = 6$).

and blood vessels in the ESWT group were found in comparison to the control group. No adverse effect of ESWT on rabbits was observed during the investigation. The preliminary data show that the formation of joint adhesion could even be avoided effectively by ESWT during the healing of knee decortication. Although ESWT

can treat the patients with fibrotic conditions to restore the ROM of the joint, it is more appreciated avoiding the occurrence of such abnormal fibrous tissues. The merits (e.g., painless and noninvasive procedure, simple operation, and fast recovery) of ESWT may be suitable for the outpatient applications. In a systematic review, it is found that early motion is safe and may help avoid problems with later arthrofibrosis [22]. Combination of ESWT with the current preventive modalities may be more effective.

Although the underlying mechanism is not fully understood, the promising outcome encourages further studies. Anti-inflammatory (e.g., reduced inflammatory cytokines) and anti-fibrotic effects (e.g., increased flexibility of the collagen fibers and tendons), soft-tissue healing, increased regional blood flow, neovascular changes, and enzyme release were found [23,24]. ESWT can change the structure or composition of capsular contracture [25]. Decreased water content, loosen structure, and less collagen deposition in the capsule wall might alleviate scar formation. High expression of the angiogenic growth factor VEGF after ESWT has been supported by immediate vasodilatation [26,27]. The expression of endothelial nitric oxide synthase was enhanced whereas the infiltration of TGF- β 1-positive cells was suppressed, up-regulating anti-inflammatory cytokines and down-regulating pro-inflammatory cytokines, respectively. ESWT may modulate endogenous nitric oxide (NO) production either under normal or inflammatory conditions as shown by the rapid enhancement of endothelial NO synthase (eNOS) and the subsequent suppression of NF- κ B [28]. eNOS may be shifted to a tyrosine-dephosphorylated form for its rapid enzyme activation but without affecting its serine-phosphorylation. ESWT may stabilize the tissue by stimulating and reactivating the healing process of the tendons and their surrounding tissues by creating new muscle fibers through facilitating the secretion of angiogenic substances around the affected region and increasing blood flow to the region [18]. Pain reduction is due to changes in the metabolism of cells and the penetrability of endothelial tissue. ESWT-induced pain relief could be attributed to hyperstimulation analgesia and neovascularization. Consequent functional gains would result from the decrease in pain and the increase in mobility.

There are some limitations to this investigation. Firstly, biological responses after ESWT are time-dependent. Progressive therapeutic effectiveness and outcome are more convincing for the future clinical trials. A large number of animals will be used in the future. More

observers will be involved for independent evaluation and the inter-observer reliability. Secondly, the operation parameters of ESWT (e.g., energy flux density, pulse repetition frequency, the number of shock waves delivered, dose, and duration of therapy) used in this study are similar to those used in the musculoskeletal diseases [17,19,29] and may not be optimal for this application. However, optimization of ESWT has not been carried out by most of the groups. Thirdly, the biochemical analysis was not evaluated for ESWT-induced bioeffects, such as the expression of eNOS, NF- κ B, TGF- β 1, fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1), and the cytokines or peptide growth factors, because an abnormal expression of these proteins may accentuate the degree of fibrous tissue formation up to 3 months after injury [3]. Finally, muscles or tendons may also become tethered to the bone by arthrofibrosis. Collagen content and type-III ratio are the key factors that determine the mechanical strength of repair tissue, and a higher proportion of type-III collagen is assumed to decrease it by reducing fibril diameter, which has an intimate correlation with the strength of connective tissue. An exaggerated synovial and inflammatory response may result in the activation and proliferation of fibroblastic cells, which produce elevated levels of type VI collagen and extracellular matrix proteins. Specific alpha-smooth muscle actin-containing fibroblastic cells play a critical role in tissue contraction associated with wound healing. Immunohistochemical staining to different tissues, such as Picrosirius red for collagen and CD31 for angiogenesis, could illustrate the morphological changes during the joint healing. A greater understanding of the pathogenesis of arthrofibrosis and related inflammatory mediators and cytokines may result in novel therapies for treating patients with arthrofibrosis.

In summary, this preliminary animal experiment confirmed the effectiveness and safety of preventing the formation of arthrofibrosis during the knee healing by extracorporeal shock wave therapy in terms of the macroscopic score of arthrofibrosis, contracture angle of the right knee, and histological observation. It shows that extracorporeal shock wave therapy has great potential for the future clinical trial to prevent the arthrofibrosis during the knee healing.

Conclusion

This preliminary animal experiment confirmed the effectiveness and safety of suppression arthrofibrosis by shock wave therapy in terms of the macroscopic score of arthrofibrosis, contracture angle of the right knee, and histological observation. It shows that shock wave therapy has great potential for the future clinical trial.

Conflict of interests

None.

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