The Safety of Extracorporeal Shockwave Therapy in Hemophilic Arthropathy

Wanshan Lo
Chang Gung Memorial Hospital Kaohsiung Branch  https://orcid.org/0000-0002-4725-7925

Jiunn-Ming Sheen
Chang Gung Memorial Hospital Kaohsiung Branch

Yu-Chieh Chen
Chang Gung Memorial Hospital Kaohsiung Branch

Kuan-Ting Wu
Chang Gung Memorial Hospital Kaohsiung Branch

Lin-Yi Wang
Chang Gung Memorial Hospital Kaohsiung Branch

Yiu-Chung Lau
Chang Gung Memorial Hospital Kaohsiung Branch

Chih-Chen Hsiao
Chang Gung Memorial Hospital Kaohsiung Branch

Jih-Yang Ko (kojy@cgmh.org.tw)
Chang Gung Memorial Hospital Kaohsiung Branch

Research article

Keywords: extracorporeal shockwave therapy, hemophilic arthropathy

DOI: https://doi.org/10.21203/rs.3.rs-181422/v1

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Abstract

Background

The hemophilic arthropathy was caused by repeated joint bleeding, which resulted in joint synovium hyperplasia, cartilage damage and bone deformity. Extracorporeal shockwave treatment (ESWT) is a non-invasive treatment with high safety and has been widely used in the treatment of various musculoskeletal conditions. This study was aimed to evaluate the safety of ESWT in hemophilic arthropathy of the knee.

Methods

This is a prospective single blind randomized control study conducted between 2019/08/01 and 2020/07/31. Hemophilia and Von Willebrand disease patients were enrolled and randomized for extracorporeal shock wave therapy to the left or right knee joint and energy-free sham therapy to the other knee joint at the 1st and 2nd month after prophylactic coagulation factor administration. As safety evaluation, hemophilia joint health score (HJHS), knee score scale (KSS), visual analog scale (VAS) and ultrasound (HEAD-US) were checked at the beginning, 1st, 2nd, 3rd and 6th month. Knee MRI was examined at the beginning and 6th month.

Results

HJHS score of the knee receiving real ESWT did not elevate in 9 patients (75%). KSS demonstrated neither significant improvement nor deterioration after ESWT. VAS declined after two sessions of ESWT. Ultrasound and MRI showed no breakthrough joint bleeding nor progression of previously existed effusion and hemarthrosis.

Conclusion

ESWT might be a safe treatment for hemophilic arthropathy once prophylactic coagulation factors are adequately administrated before ESWT. Further well-controlled study enrolling more hemophilia patients might be needed for the effectiveness of ESWT on these patients.

Introduction

Hemophilia is a disease of congenital coagulation dysfunction. Because of its sexually linked inherited characteristics, most patients are male. The incidence is one in 10,000. Its severity can be divided into mild, moderate, and severe depending on the deficiency of coagulation factors. Patients of severe hemophilia are severely deficient in coagulation factors and spontaneous joint or muscle bleeding often occurs. As to current treatment for severe hemophilia patients, coagulation factors are administrated regularly as prophylaxis rather than administrated as on demand [1].

The most common sites of bleeding in hemophilia patients are in the musculoskeletal system, especially the knee and ankle joints. Repeated joint bleeding resulted in joint synovium hyperplasia, cartilage
damage, bone destruction, spurs, joint swelling and deformation. The condition was called hemophilic arthropathy. The pain, stiffness and limited motion caused by the diseases often cause walking disorders and inconvenience in daily activities and seriously deteriorate the hemophilia patients’ quality of life. Arthropathy caused by recurrent joint bleeding is now regarded as a serious complication due to the increased life span of hemophilia patients. Studies in Europe and the United States have found that the health-related quality of life of hemophilia patients is related to joint disease.

Extracorporeal shockwave treatment (ESWT) is a non-invasive treatment with high safety, which has been widely used in treatment of various musculoskeletal conditions including Achilles tendinitis, plantar fascilitis and tennis elbow [2-9]. The proposed mechanisms of ESWT include promotion of neovascularization at the tendon-bone junction, stimulating proliferation of tenocytes and osteoprogenitor differentiation, increasing leukocyte infiltration, amplifying growth factor and protein synthesis to stimulate collagen synthesis and tissue remodeling. Nevertheless, ESWT has certain contraindications including uncorrected coagulation abnormalities [10]. Therefore, ESWT had very limited use in hemophilia patients. The main purpose of this study was to evaluate the safety of extracorporeal shock wave as a treatment for hemophilic arthropathy of the knee.

Method

This is a prospective single blind randomized control study conducted between 2019/08/01 and 2020/07/31 (IRB number: 201800486B0C601 and 201900209B0A3). Hemophilia patients elder than 20-year-old were enrolled. Patients who had acute joint bleeding episodes were excluded.

All the patients were randomized for extracorporeal shock wave therapy to the left or right knee joint and energy-free sham therapy to the other knee. The treatments were performed by a senior specialist at the 1st and 2nd month. The ESWT treatment site was at the musculo-tendonous junction of the quadriceps tendon. As to the energy of ESWT, the chosen knee received 3000 shocks with the energy of 0.2mJ / mm2 by Storz Medical Duolith SD1® and the treatment duration was 15 minutes each time.

Since uncorrected coagulation abnormalities is regarded as a contraindication for ESWT, prophylactic coagulation factors were administrated before each treatment. The concentration of blood clotting factor was expected to be increased up to at least 60%.

As safety evaluation, hemophilia joint health score (HJHS) [12], knee society score (KSS) [13], visual analog scale (VAS) [14] and ultrasound (HEAD-US) [11] were checked at the beginning and then at 1st, 2nd, 3rd and 6th month for every patient. In other words, the 2nd month HJHS, KSS, VAS and ultrasound were calculated one month after 1st ESWT while the 3rd month HJHS, KSS, VAS and ultrasound were calculated one month after the second ESWT. The 6th month HJHS, KSS, VAS and ultrasound were calculated 3 months after completing two sessions of ESWT. Knee MRI was performed at the beginning and at the 6th month.
Hemophilia joint health score (HJHS) [12] is an evaluation tool of bilateral joints related to swelling (0 to 3 points), duration (0 or 1 point), muscle atrophy (0 to 2 points), crepitus on motion (0 to 2 points), flexion loss (0 to 3 points), extension loss (0 to 3 points), joint pain (0 to 2 points) and strength (0 to 4 points). Higher score indicates worse clinical conditions. Originally the score summary included bilateral elbows, knees, ankles and the global gait score (walking, stairs, running, hopping on one leg). Bilateral joints are evaluated separately. In this study, only the scores of right and left knees were calculated. Knee score scale (KSS) [13] includes evaluating objective knee indicators and functional activities. The objective knee indicators are composed of evaluating alignment, instability, joint motion by doctors and evaluating symptoms, satisfaction, and expectations by hemophilia patients. The functional activities evaluation was performed by the patients and included walking and standing, standard activities, advances activities and discretionary knee activities. In both parts of KSS evaluation, higher score indicates better clinical conditions.

The ultrasound (HEAD-US) evaluation was composed of two parts including disease activity (synovitis; 0 to 2 points) and osteochondral damage (cartilage: 0 to 4 points, bone: 0 to 2 points) [11]. High score indicates severe synovitis, destructions of cartilage or deranged subchondral bone. The scoring scale included evaluation of bilateral elbows, knees and joints. Only scores of disease activity of knee were taken into evaluation in this study.

Adverse event included local redness, swelling and pain evaluated by physical examination as well as breakthrough knee joint bleeding evaluated by ultrasound. The whole study for each enrolled patient took 6 months.

The statistical analysis was performed with unpaired T-test and Mean±SEM by GraphPad PRISM® version 6.01.

Results

Baseline characteristics of the study population

In the study period, 13 patients were enrolled at first. However, during the first month 1 severe hemophilia A patient was excluded due to acute bleeding of knee joint before first ESWT. Among the 12 patients who completed the study, 11 were male and 1 was female. 10 patients were diagnosed as hemophilia A, including 8 severe type and 2 mild type. The rest two patients were diagnosed as severe hemophilia B and von Willebrand disease. The above patients diagnosed as severe hemophilia received prophylactic coagulation factor administration while those diagnosed as mild hemophilia received coagulation factor treatment on demand. Half of the 12 patients had total knee replacement surgery before this study, including 6 unilateral and 1 bilateral. The 12 patients were recorded as HE01 to HE 13 (HE05 excluded). Their baseline characteristics and the knee receiving real energy ESWT were listed on Table 1.

Safety evaluation
Hemophilia joint health score (HJHS) (Fig 1.)

In 9 out of 12 patients (75%) the hemophilia joint health score of the treatment side did not elevate after ESWT treatment. On the other hand, there was no significant difference in comparison of HJHS for the treatment side before and after ESWT treatment.

Knee society score (KSS) (Tab 2,3, Fig 2,3)

There were no significant differences comparing pre-ESWT status (0 month) to post-ESWT status at 2\textsuperscript{nd} month, 3\textsuperscript{rd} month, 6\textsuperscript{th} month.

Visual analog scale (VAS) score (Fig 4.)

Comparing visual analog scale (VAS) difference at 2\textsuperscript{nd}, 3\textsuperscript{rd} and 6\textsuperscript{th} month with the pre-ESWT status (0 month) revealed significant VAS improvement at 3\textsuperscript{rd} month (-1.333 ± 0.5946, n=12, p=0.0465), after the patients’ receiving two sessions of ESWT.

Ultrasound (HEAD-US) (Fig 5.)

In 5 out of 12 patients, the disease activity score elevated one month after first ESWT. Nevertheless, after second ESWT, in 3 of the above 5 patients the disease activity score dropped. Overall speaking, comparing to pre-ESWT status, the disease activity score did not elevate in 10 out of 12 patients at the last evaluation.

Knee MRI

Despite the original study design, 5 out of 12 patients failed to complete knee MRI evaluation for the treatment site in the 6\textsuperscript{th} month. Among those 7 patients who received MRI evaluation at the beginning and at the 6\textsuperscript{th} month of the study, 4 patients had small amount effusion or hemarthroses at the beginning. After two sessions of ESWT, half of the effusion or hemarthrosis persisted without progression at the 6\textsuperscript{th} month follow-up and the effusion or hemarthrosis subsided in the other half of the patients. As to the 3 patients who had no effusion or hemarthrosis in the beginning, 1 of them developed small amount of effusion or hemarthrosis at 6\textsuperscript{th} month.

Adverse events

In 8 out of 12 patients, local redness, swelling and pain after ESWT were found but subsided within 5 to 7 days. These 8 patients were severe hemophilia A patients. No breakthrough knee joint bleeding episode was found.

Discussion
Extracorporeal shockwave treatment (ESWT) has been widely used in treatment of various musculoskeletal conditions. Hemophilic arthropathy was not one of the indications of ESWT, probably due to the concern of coagulation abnormality. In this study, prophylactic coagulation factors were administrated before ESWT, with the doses calculated according to each patient’s body weight and their baseline coagulation factor instructions. The serum concentration of coagulation factors was estimated to be elevated to at least 60%, which was sufficient for avoiding joint or muscle bleeding. According to our knowledge, this was the first study to suggest the safety of ESWT application in the knee joint of hemophilia patients.

For safety evaluation, 9 out of 12 patients (75%) whose HJHS did not elevate after ESWT, which indicated that their joint health was not worsen by the ESWT intervention. VAS was also used for evaluating patients’ severity of pain. We compared the difference between VAS after ESWT and before ESWT (0 month). At the 3rd month, after the patients’ receiving second ESWT in the previous month, the difference of VAS became obvious. In the following three months, the VAS scores started to rise. This might indicate the improvement of joint pain after ESWT. More frequent ESWT might be required for better treatment outcome and joint pain relief. As to KSS, both objective knee indicators and functional activities scores showed no significant differences comparing pre-ESWT status (0 month) to post-ESWT status at 2nd month, 3rd month, 6th month. This finding demonstrated absence of markable worsening after ESWT compared to patients’ baseline condition.

Serial ultrasound examinations were arranged and none of them reported acute knee joint bleeding. HEAD-US [11] ultrasound was viewed as a useful and real-time tool for evaluating hemophilic arthropathy. However, in this study the overall difference in serial follow-up for each patient was unmarkable. Since the scoring scale are made of disease activity (synovitis) as well as osteochondral damage evaluation, the score might be interfered by the patients’ baseline joint condition and their total knee replacement history.

Knee MRI evaluation was limited to its availability and the result would be interfered by artificial joint. Nevertheless, in the 7 patients who received knee MRI examination before and after ESWT, only one patient had newly developed small amount effusion or hemarthrosis. The knee joint condition of the other 6 patients remained stable or improved after ESWT.

**Limitation**

Though generally the above results reported it was relatively safe when using extracorporeal shockwave therapy under the dosage of 3000 shocks with the energy of 0.2mJ / mm2 as a treatment for hemophilic arthropathy, this study was limited largely by case numbers. For better evaluation of safety in ESWT for hemophilic arthropathy, larger trial enrolling more hemophilia patients might be needed. In this study, the follow-up period was limited as well. For better evaluation of ESWT use in hemophilic arthropathy, longer follow-up time is needed. As to evaluation of effectiveness, baseline characteristics of hemophilia patients such as hemophilia type, severity, comorbidities, obesity and joint replacement history shall be
taken into consideration [16]. Once safety of ESWT use in hemophilic arthropathy is assured, titration of ESWT energy might be considered for better treatment outcome [3, 17].

**Conclusion**

This study concluded that extracorporeal shockwave therapy under the dosage of 3000 shocks with the energy of 0.2mJ / mm2 was safe for hemophilia patients. No breakthrough bleeding was noted in the treatment cases. ESWT might be a safe treatment for hemophilic arthropathy once prophylactic coagulation factors are adequately administrated before ESWT. Further well-controlled study enrolling more hemophilia patients might be needed for the effectiveness of ESWT on these patients.

**Abbreviations**

ESWT: Extracorporeal shockwave therapy  
HJHS: Hemophilia joint health score  
KSS: Knee score scale  
VAS: Visual analog scale  
HEAD-US: Haemophilia Early Arthropathy Detection with Ultrasound  
MRI: Magnetic Resonance Imaging  
SEM: Standard error of the mean

**Declarations**

**Acknowledgments**

The study was sponsored by grants CMRPG8J0171, CRRPG8J0071, CRRPG8J0072, CRRPG8J0073 from Chang Gung Medical Foundation. We are thankful for the help of the Center for Shockwave Medicine and Tissue Engineering, Department of Medical Research, Kaohsiung Chang Gung Memorial Hospital, Taiwan and for the founder of the center, Prof. Ching-Jen Wang

**Ethics approval and consent to participate**

This study was approved by Chang Gung Medical Foundation Institutional Review Board. This study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participants in this study.

**Consent for publication**
Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Competing interests

The authors declared that they did not receive any financial payments or other benefits in writing this manuscript. No benefit was received or will be received directly or indirectly from a commercial entity related to the performance of this study.

Funding

This study did not receive any specific grant from any funding agencies in the public, commercial, or not-for-profit sectors.

Authors’ contributions

KJY designed the study; SJM, CYC, WKT, WLY, LYC and LWS interpreted the data; LWS prepared the draft manuscript; HCC and KJY were responsible for ensuring the integrity of the data analysis. All authors read and approved the manuscript.

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**Tables**
Table 1.
Baseline characteristics of 12 patients

| No. | Gender | Age | Type of hemophilia | Severity | Baseline coagulation factor | Real energy ESWT | Total knee replacement history |
|-----|--------|-----|-------------------|----------|-----------------------------|------------------|-------------------------------|
| HE 01 | male | 47 | Hemophilia A | severe | Adynovate® | Left | Right |
| HE 02 | male | 32 | Hemophilia A | severe | Adynovate® | Right | Left |
| HE 03 | male | 54 | Hemophilia A | mild | Kogenate® | Right | |
| HE 04 | male | 42 | Hemophilia B | severe | Rixubis® | Right | Left |
| HE 05 | male | 32 | Hemophilia A | severe | Nuwiq® | Right | Left |
| HE 06 | male | 34 | Hemophilia A | severe | Nuwiq® | Right | Left |
| HE 07 | male | 36 | Hemophilia A | mild | Advate® | Left | |
| HE 08 | female | 29 | von Willebrand disease | | Alphnante® | Right | |
| HE 09 | male | 45 | Hemophilia A | severe | Adynovate® | Right | Bilateral |
| HE 10 | male | 35 | Hemophilia A | severe | Eloctate® | Left | |
| HE 11 | male | 39 | Hemophilia A | severe | Eloctate® | Right | Left |
| HE 12 | male | 29 | Hemophilia A | severe | Nuwiq® | Left | |
| HE 13 | male | 29 | Hemophilia A | severe | Nuwiq® | Left | |
Table 2.
Comparing knee society score (objective knee indicators) of pre-ESWT (0 month) status to post-ESWT status at 2\(^{nd}\) month, 3\(^{rd}\) month, 6\(^{th}\) month

|            | Pre-ESWT | 2\(^{nd}\) month | 3\(^{rd}\) month | 6\(^{th}\) month |
|------------|----------|-------------------|------------------|-----------------|
| Mean ±SEM  | 95.00 ± 5.677 | 92.75 ± 6.388    | 91.00 ± 5.835    | 88.17 ± 5.180   |
| n          | 12       | 12                | 12               | 12              |
| p          | 0.7948  | 0.6280            | 0.3836           |

Table 3.
Comparing knee society score (functional activities) of pre-ESWT (0 month) status to post-ESWT status at 2\(^{nd}\) month, 3\(^{rd}\) month, 6\(^{th}\) month

|            | Pre-ESWT | 2\(^{nd}\) month | 3\(^{rd}\) month | 6\(^{th}\) month |
|------------|----------|-------------------|------------------|-----------------|
| Mean ±SEM  | 76.50 ± 4.869 | 75.08 ± 4.401    | 76.42 ± 4.570    | 73.42 ± 5.140   |
| n          | 12       | 12                | 12               | 12              |
| p          | 0.8311  | 0.9902            | 0.6674           |