Original Article

Effect of Pulsed Electromagnetic Fields on Clinical Signs and Quality of Life in Patients with Hemophilic Arthropathy of the Knee Joint: A Randomized Controlled Trial

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Abstract

Background: Hemophilic arthropathy (HA) causes severe joint damage and impairs the quality of life (QoL) of hemophiliacs. This study was undertaken to evaluate the effect of pulsed electromagnetic fields (PEMFs) on the clinical signs and QoL of patients with severe hemophilia A experiencing moderate HA in the knee joint. **Materials and Methods:** Thirty-six severe hemophiliacs with HA of the knee joint were randomly assigned into the PEMF (n = 20) or placebo (n = 16) groups. The PEMF group received 60 min of PEMF (2 Hz, 25 Gauss for 30 min and 70 Hz, 30 Gauss for 30 min) on the knee joint, three times per week for 6 weeks. The clinical signs, QoL, and pain intensity were measured by the Hemophilia Joint Health Score, A36 Hemofilia-QoL Questionnaire, and visual analog scale, respectively, before and after treatment. **Results:** In the PEMF group, a significant difference before and after intervention in terms of clinical signs, QoL, and pain intensity ($P < 0.05$) was founded. Between-group analysis showed a significant improvement in clinical signs (except for atrophy, strength, and swelling duration), QoL, and pain intensity in the PEMF versus control group ($P < 0.05$). **Conclusions:** PEMF can improve the clinical signs, QoL, and pain intensity of severe hemophilia A patient with moderate knee hemophilic arthropathy.

Keywords: *Clinical signs, hemophilia A, hemophilic arthropathy, pain intensity, pulsed electromagnetic fields, quality of life*

Introduction

Hemophilic arthropathy (HA), a major problem for hemophiliacs, is a progressive joint damage caused by repeated spontaneous hemarthrosis.[1] In hemarthrosis, iron is deposited in the synovial membrane and causes hyperplasia and hypertrophy of the synovial membrane. Iron also can cause inflammation of the synovial membrane, leading to damage to the cartilage via inflammatory cytokines. On the other hand, the presence of blood in the joint space has a direct effect on the cartilage that results in chondrocyte apoptosis and cartilage destruction.[2,3] The unique anatomical features of the articular surfaces and the important role in weight-bearing of the knee make it highly prone to HA.[1,4] Knee HA can cause chronic pain, limited range of motion (ROM), crepitus, muscle weakness, deformity, and ankylosis, which in turn decreases activity in the patients and ultimately affects their QoL.[2]

The main treatment for hemophilia is the replacement therapy of deficient coagulation factors, which is carried out through prophylaxis (preventive) and on-demand (episodic) methods.[1] The ideal recommended treatment is the prophylaxis method. Because of high cost of treatment, the current method in developing countries is on-demand, only in the case of bleeding. On the other hand, in developed countries, despite the notable successes of prophylaxis in the prevention of hemarthrosis, it has not been fully able to prevent HA, which still remains a major problem for hemophiliacs.[5,6] In parallel with replacement therapy, physiotherapy is a basic requirement for hemophiliacs. Physiotherapy can reduce swelling and pain, maintain ROM and muscle strength, improve balance and proprioception, and prevent further damage to joints.[2,7]

Pulsed electromagnetic field (PEMF) is a nonthermal, noninvasive, safe, and low-cost modality in physiotherapy.[8] The cellular

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membrane assumed the primary target of the magnetic field action. The suggested mechanism of action of the magnetic fields is through affecting the signal transaction pathways by the alteration of ion binding and transport.[9] PEMF has several biological effects such as vasodilatation, increasing tissue oxygenation, and improving membrane potential function and ion exchange.[10,11] These biological effects could reduce pain and inflammation and enhance blood circulation and bone unification. PEMF is also useful in the treatment of chronic pain caused by connective (cartilages, tendons, ligaments, and bones) and soft tissue injuries. PEMF may mimic the effects of mechanical stimuli which could be useful for those individuals who cannot exercise readily without pain.[12] Hence, as hemophilia patients are afraid of of re-bleeding due to intense physical activity they may benefit from PEMF application.

Few studies have examined the effects of PEMF on musculoskeletal problems in hemophiliacs.[13-15] None of these studies have examined the effect of this modality on the improvement of clinical signs and QoL in HA of the knee joint by using valid hemophilia-specific tools and by applying different therapeutic frequencies. Therefore, the aim of the current study was to evaluate the effect of PEMF on the clinical signs and QoL of severe hemophilia A patients with HA of the knee joint. Our hypothesis was that the PEMF can improve clinical signs (swelling, muscle atrophy, crepitus on motion, joint pain, ROM, muscle strength, and global gait), QoL, and pain intensity of severe hemophilia A patients with HA of the knee joint.

Materials and Methods

Subjects and design

This randomized controlled trial was conducted on patients with severe hemophilia A with HA of the knee joint who referred to the Isfahan Province Hemophilia Center (affiliated to Seyed-al-Shohada Hospital) in Isfahan, Iran. The sampling method was simple random sampling. The participants were 40 males with severe hemophilia A (coagulation factor VIII levels <1%), aged 20–40 years, with active synovitis (having target joint) of the knee joint who also suffered from moderate HA of the knee joint based on the Pettersson radiographic criteria (score 5–9).[16] In the cases that the both knee fulfill the mentioned criteria, we selected the knee with higher Pettersson score as the target knee for the treatment.

The exclusion criteria were patients having a history of an inhibitor, body mass index (BMI) >30 kg/m^2, heart pacemaker, having had knee joint replacement surgery or intra-articular injection of the knee in the last 6 months, knee physiotherapy in the past month, or the presence of more than 30° of knee flexion contracture. In addition, during the study, patients who used anti-inflammatory or analgesic drugs and those experiencing the occurrence of hemarthrosis or acute knee joint symptoms were excluded from the study. This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences in Tehran, Iran (ethics code: IR.SBMU.RETECH.REC.1397.547). Further, the study was registered in the Iranian Registry of Clinical Trials (IRCT) with the code of IRCT20180716040488N1.

Among 350 men with severe hemophilia A which registered in Isfahan Province Hemophilia Center, after informing about the study conditions by the staffs of the center, 310 of them were excluded from the study because they did not meet the inclusion criteria. Ultimately, 40 patients were included for the study. Figure 1 shows the study design and the flow of participants. All participants signed informed consent form and were randomly assigned to either the PEMF (n = 20) or placebo (n = 20) groups by using random-number table method. Knee joint clinical signs, pain intensity, and QoL of the individuals were measured before and after 18th sessions. Patients were blinded to their treatment allocation and were not informed about the randomization procedure. None of the participants were aware of the on or off status of the electromagnetic device. Our device causes no sounds or sensations for the patient during exposure, and the other treatment protocols were the same in both groups. However, the investigator was not masked to the group assignment.

Sample size calculation

To calculate the sample size, suggested formula for parallel-design randomized controlled trial was used based on a = 0.05, 90% power, and a standardized effect size = 0.025 based on total score of Hemophilia Joint Health Score (HJHS) as a key variable.[14] We reached to 20 participants per group.

Therapeutic regimen

The PEMF was administered by magnetic device (Fisioline s.r.1 Fisiofield Maxi, Verduno, Italy) that was calibrated before intervention. This device causes no sounds or sensations for the patient during exposure. The PEMF treatment included 30 min of treatment at frequency of 2 Hz and an intensity of 25 Gauss with a rectified sinusoidal waveform. After a 10-min interval, the treatment continued for 30 min at frequency of 70 Hz and an intensity of 30 Gauss with a square waveform (1 h total exposure). The placebo group underwent the same plan while the device was switched on, but the output was zero. The treatment was received three times per week for 6 weeks. In each session, the patient reclined in a supine position with a cushion was under their semi-flexed knees. The patient was asked to remove any metal devices and inform the therapist of any annoying sensation. The 60-cm solenoid of the device was placed around the knee, and after adjusting the required parameters, the device was turned on. Before each session, patients received 20 IU/kg of coagulation factor VIII.

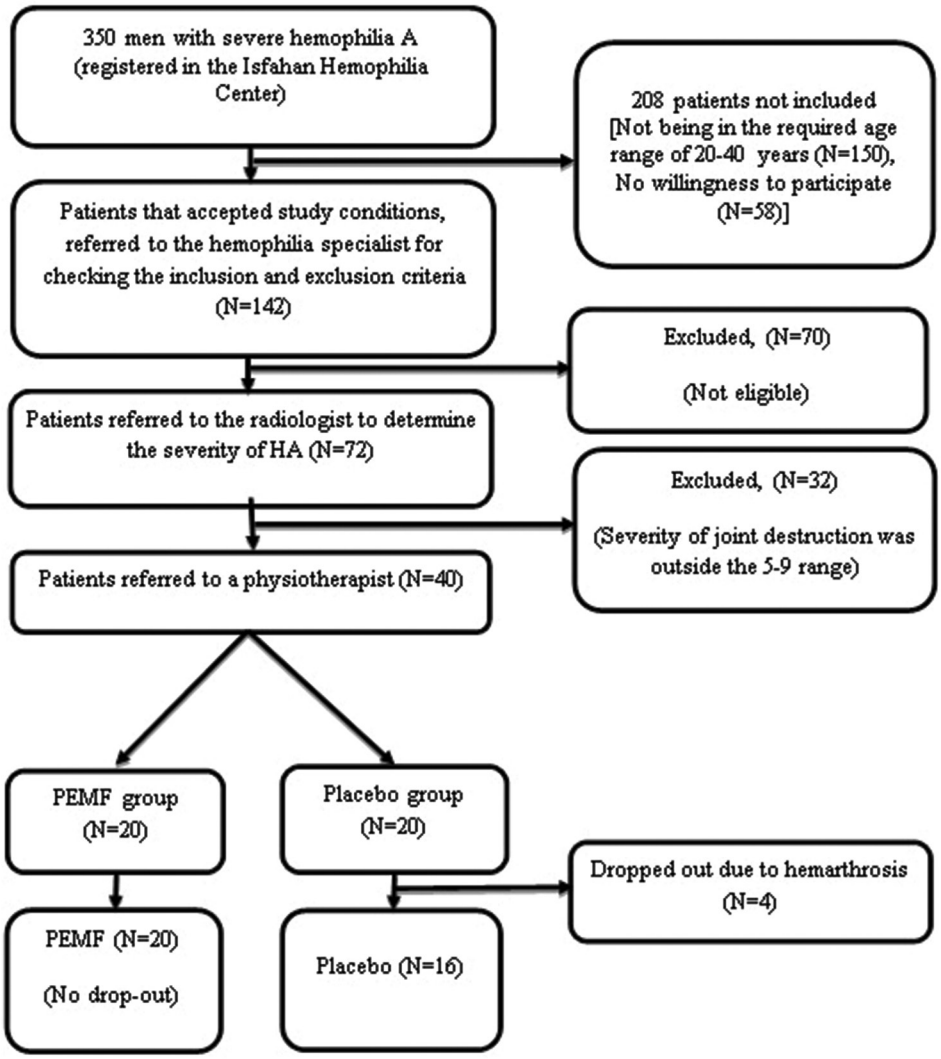

Figure 1: The experimental design of the study and participants flow

Variables assessment

The demographic data were collected by a physiotherapist at the beginning of the study. At baseline, lateral and anteroposterior radiographic views of the knee joint were taken, and the severity of the HA of the joint was measured by a radiologist using Pettersson-specific radiographic criteria as approved by the World Federation of Hemophilia. This scale precisely discriminates between the different stages of HA. It surveys eight joint features: osteoporosis, enlargement of epiphyses, irregular subchondral surface, narrowing of joint space, subchondral cyst formation, erosion of joint margins, gross incongruence of articulating bone ends, and joint deformity. The highest score of 13 indicates complete joint destruction.[17,18]

The clinical signs, pain intensity, and QoL were measured before the first session and after the last session of treatment. The visual analog scale (VAS) was used to determine the pain intensity (0 = no pain to 10 = most severe pain). The validity and reliability of the scale have been approved for the assessment of pain intensity in knee disorders.[19]

The clinical signs of the knee joint were evaluated using the HJHS 2.1 developed by the International Prophylaxis Study Group.[20] The HJHS is increasingly used in the studies of hemophilic children and adults to evaluate joints.[21] It comprises eight items about joints (swelling, duration of swelling, muscle atrophy, crepitus on motion, flexion loss, extension loss, joint pain, and muscular strength). The score of each joint ranges from zero (no damage) to 20 (highest joint damage). A separate item for global gait examines walking, stairs, running, and hopping on one leg and is scored from zero (all skills are within normal limits) to 4 (no skills are within normal limits). In this study, we just evaluated the knee joint. The total score is obtained by summing the knee joint totals and the global gait score.[18,20] The HJHS was filled in by a physiotherapist based on the HJHS manual and supporting HJHS instructional video. The validity and reliability of

the HJHS have been investigated by Feldman *et al*.[22] and Hilliard *et al*.[23] The HJHS showed acceptable external intraclass correlation coefficients (ICC = 0.89) and internal (Cronbach's alpha = 0.86) reliability.

The A36 Hemofilia-QoL questionnaire was used to assess the QoL of hemophiliacs.[24] It is designed for patients aged over 17 years and was used with the permission of its developer, Eduardo Remor. The original version of A36 Hemofilia-QoL was translated into Persian under the standard conditions and has been approved by the original developer. It includes 36 four-option questions to be answered by the patient. The items of A36 Hemofilia-QoL are designed in accordance with the main problems of the patients in the nine dimensions of physical health, daily activities, joint damage, pain, treatment satisfaction, treatment difficulties, emotional functioning, mental health and relationships, and social activity. A high score indicates a better QoL. The psychometric properties of the questionnaire have been investigated in previous studies that have reported acceptable validity and reliability (Cronbach's alpha = 0.925).[25,26]

Statistical analysis

Statistical analyses were based on the data which derived from per-protocol participants. The per-protocol analysis included only those participants who completed the intervention. Normality of continuous variables was evaluated using Kolmogorov–Smirnov test and Q–Q plot. The data were presented as mean (standard deviation [SD]), median (range), and frequency (percentage) for quantitative and qualitative variables. Participants' basic characteristics in the two groups were compared using independent *t*-test. To test our hypothesis that intervention improves main outcomes in patients, intra- and intergroup changes were compared by repeated-measure analysis of variance, paired *t*-test, or Wilcoxon signed-rank test, as appropriate. McNemar and Chi-square tests were used for qualitative variables. Effect size was computed using partial eta-squared for normal variables. Effect sizes for nonnormal variables were based on r = Z/SQRT (n). SPSS statistical software version 21 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, and $P < 0.05$ was considered statistically significant.

Results

Forty patients (20 in each group) with severe hemophilia A were included in this study. A total of 36 patients completed the study over the course of 8 months. Four patients in the placebo group failed to complete the study due to hemarthrosis as a result of trauma. Hence, the percentage of adherence was 100% and 80% in the intervention and control groups.

The mean (SD) age of the patients in the PEMF and control groups was 32.60 (6.07) and 29.75 (5.03) years, respectively ($P = 0.141$). The mean BMI of the participants was about 23 kg/m^2, and there were no significant differences between groups ($P = 0.766$). There also were no significant differences between groups at baseline in terms of Pettersson score ($P = 0.412$) [Table 1].

Comparison of the clinical signs, pain intensity, and QoL of the participants before and after intervention is presented in Tables 2 and 3. There were no significant differences between groups in terms of the aforementioned variables at baseline.

There were no significant differences in terms of studied variables in the control group before and after intervention, except for total QoL. The total QoL score of patients in the control group decreased significantly compared to baseline ($P = 0.038$). The total QoL score of patients treated with PEMF before and after intervention was 76.05 (21.29) and 101.80 (15.98), respectively, which showed a highly significant increase after treatment ($P < 0.0001$). There was a significant decrease in the variables of flexion loss, extension loss, joint pain, crepitus on motion, swelling, gait, VAS, and sum of joint totals in the PEMF group after treatment ($P < 0.05$). There were no significant differences in terms of strength, muscle atrophy, and duration of swelling before and after intervention in the PEMF group. The HJHS total scores in the PEMF group before and after intervention were 14.60 (2.58) and 9.65 (3.15), respectively, which showed significant decreases after treatment ($P < 0.0001$). The between-group analysis showed a significant difference between the PEMF and control subjects in terms of change in all the studied variables, except for strength, muscle atrophy, and duration of swelling ($P < 0.05$). These differences were highly significant in the total score for QoL (η_p^2=0.822), HJHS total score (η_p^2=0.903), pain, extension loss, crepitus on motion, VAS (η_p^2=0.782), and sum of joint totals (η_p^2=0.775) ($P < 0.001$) [Tables 2 and 3].

Discussion

The present study investigated the effect of PEMF on clinical signs (swelling, muscle atrophy, crepitus on motion, joint pain, ROM, muscle strength, and global gait), pain intensity, and QoL with regard to HA of the knee joint. The results of this study showed that PEMF can significantly reduce swelling, pain, and crepitus and improve flexion and extension ROM, gait, and QoL in patients with moderate HA of the knee.

The results of this study show that PEMF significantly decreased knee joint swelling in patients with hemophilia.

Table 1: Demographic data and baseline characteristics

Variables	Case (*n*=20)	Control (*n*=16)	*P**
Age	32.60 (6.07)	29.75 (5.03)	0.141
BMI	23.21 (3.16)	23.54 (3.51)	0.766
Pettersson score	5.60 (1.57)	6.06 (1.77)	0.412

Values are mean (SD); *P* values resulted from independent *t*-test. SD: Standard deviation, BMI: Body mass index

Table 2: The clinical signs, pain intensity, and quality of life before and after intervention

	Case (*n*=20)			Control (*n*=16)			*P***	*P****	Effect size
	Before	After	*P**	Before	After	*P**			
Swelling									
Mean (SD)	0.80 (0.77)	0.45 (0.69)	0.008	1.13 (1.09)	1.13 (1.09)	>0.05	0.459	0.009	−0.43
Median (range)	1 (0–2)	0 (0–2)		1 (0–3)	1 (0–3)				
Duration of swelling, *n* (%)									
0	8 (40)	8 (40)	>0.0.05	6 (37.5)	6 (37.5)	>0.05	0.878	0.88	-
1	12 (60)	12 (60)		10 (62.5)	10 (62.5)				
Muscle atrophy									
Mean (SD)	1.40 (0.75)	1.40 (0.75)	>0.0.05	1.38 (0.62)	1.38 (0.62)	>0.05	0.789	>0.05	-
Median (range)	2 (0–2)	2 (0–2)		1 (0–2)	1 (0–2)				
Crepitus on motion									
Mean (SD)	1.55 (0.51)	1.00 (0.86)	0.001	1.50 (0.63)	1.50 (0.63)	>0.05	0.503	<0.001	−0.59
Median (range)	2 (1–2)	1 (0–2)		2 (0–2)	2 (0–2)				
Flexion loss									
Mean (SD)	1.55 (1.28)	1.35 (1.27)	0.046	1.19 (1.28)	1.25 (1.29)	0.317	0.479	0.034	−0.35
Median (range)	2 (0–3)	1.5 (0–3)		1 (0–3)	1 (0–3)				
Extension loss									
Mean (SD)	1.75 (0.97)	1.25 (1.07)	0.004	1.50 (1.10)	1.50 (1.10)	>0.05	0.519	<0.001	−0.51
Median (range)	2 (0–3)	1 (0–3)		2 (0–3)	2 (0–3)				
Joint pain									
Mean (SD)	1.70 (0.47)	0.20 (0.41)	<0.001	1.50 (0.73)	1.50 (0.73)	>0.05	0.265	<0.001	−0.91
Median (range)	2 (1–2)	0 (0–1)		2 (0–2)	2 (0–2)				
Strength									
Mean (SD)	1.50 (0.89)	1.50 (0.89)	>0.05	1.50 (0.89)	1.50 (0.89)	>0.05	0.741	>0.05	-
Median (range)	2 (1–2)	1.5 (0–4)		2 (0–3)	2 (0–3)				
Global gait									
Mean (SD)	4.00 (0.00)	1.95 (0.22)	<0.001	3.69 (0.60)	3.69 (0.60)	>0.05	0.211	<0.001	−0.97
Median (range)	4 (4–4)	2 (1–2)		4 (2–4)	2 (2–4)				

**P*-values resulted from paired *t*-test, Wilcoxon signed-rank test or McNemar test; ***P*-values are based on comparison of variables in baseline and resulted from independent *t*-test, Mann–Whitney, or Chi-square tests; ****P*-values are based on comparison of changes of variables after intervention and resulted from independent *t*-test, Mann–Whitney, or Chi-square tests. SD: Standard deviation

Table 3: Mean (standard deviation) score of quality of life, Hemophilia Joint Health Score, and visual analog scale at the baseline and after 6 weeks of intervention in two studied groups

	Case (*n*=20)			Control (*n*=16)			*P* value time×group	Observed power	Partial Eta-squared (η2ρ)
	Baseline	End of study	*P**	Baseline	End of study	*P**			
Sum of joint totals	10.6 (2.58)	7.7 (3.05)	<0.001	10.37 (4.33)	10.5 (4.27)	0.164	<0.001	1	0.775
HJHS total score	14.60 (2.58)	9.65 (3.15)	<0.001	14.06 (4.57)	14.19 (4.52)	0.164	<0.001	1	0.903
VAS	5.18 (1.77)	1.33 (1.44)	<0.001	5.00 (2.56)	5.19 (2.71)	0.196	<0.001	1	0.782
QoL total score	76.05 (21.29)	101.80 (15.98)	<0.001	78.19 (18.68)	75.75 (19.81)	0.038	<0.001	1	0.822

**P*-values resulted from paired *t*-test, ***P*-values are based on repeated-measures ANOVA. ANOVA: Analysis of variance, HJHS: Hemophilia Joint Health Score, VAS: Visual analog scale, QoL: Quality of Life

Eid and Aly[13] reported similar results suggesting that PEMF can effect swelling of the knee joint in children with hemarthrosis due to its positive anti-inflammatory effects, which can reduce pain and improve function.[13] Several researches have shown that PEMF has a direct effect on reducing inflammatory markers. This may relate to increased expression and function of the adenosine A2a receptors and decreased lysosomal enzyme activity and TNF-α, IL-1β, IL-6, and PGE2 levels.[27-29] PEMF can also be effective on the calcium/calmodulin-dependent nitric oxide (NO) signaling pathway to reduce inflammation by altering the secretion of NO as a major vasodilator.[30]

PEMF significantly reduced knee pain after 6 weeks. These results are in line with the results of other surveys.[13-15] Parhampour *et al*.[14] studied patients with severe hemophilia and osteoporosis and reported decreased knee and ankle pain even with the application of PEMF to the pelvic region. Pain in severe arthropathy occurs because of inflammatory factors, increased pressure on articular

surfaces, contractures, muscle shortness, and capsule stretch.[31] The analgesic effect of PEMF is supposed to be due to its anti-inflammatory effects.[11,13] PEMF also reduces pain by modulating the cell membrane potential and increasing the pain threshold. This may stem from extended action of endorphins over enkephalins without affecting the thermal sensory threshold.[8,15,32]

Similar to the findings of previous studies, PEMF to the knee in the current study significantly improved flexion and extension ROM.[13,15] In contrast, Parhampour *et al*.[14] reported that ROM of the knee did not change significantly after treatment. However, in their study, PEMF was applied to the pelvic region. It could be expected that its effect on the knee may not be noticeable because it was not directly applied to the knee. In fact, improvement in stiffness is caused by enhanced blood circulation in the periarticular compartment, improved growth of chondrocytes, and the positive effect of PEMF on cartilage differentiation. PEMF activates NO synthase, which increases blood circulation in the endothelial cells. It also increases *in vivo* and *in vitro* angiogenesis through the endothelial release of fibroblast growth factor-2.[33,34]

In the present study, significant improvements were observed in joint crepitus after PEMF treatment which is likely the results of its positive effect on the articular cartilage. *In vitro* studies on osteoarthritis (OA) models indicate that PEMF could increase transforming growth factor-β (TGFβ), which activates chondrocytes. TGFβ leads to proanabolic (increased expression of aggrecan and collagen) and anticatabolic (decreased matrix metalloproteinase and IL-1β and increased inhibitor of matrix metalloproteinase) activities within the cartilage, which affects the homeostasis of the cartilage and delays OA development.[29,35,36]

This study demonstrated a positive effect for PEMF on the gait. In line with these results, Tiktinsky *et al*.[15] reported improvement in walking ability after treatment with PEMF. Parhampour *et al*.[14] reported less pain and more ease in using stairs, galloping, and running slowly after 6 weeks of PEMF therapy. Eid and Aly[13] also reported that the increased distance in 6-min walk test in the PEMF group reflected the positive effect of PEMF on mobility and physical fitness in children with hemophilia. Improvement in gait can be explained by the reduction in pain, inflammation, and stiffness and enhancement of ROM.

Another finding of this study is the positive effect of PEMF on the QoL of patients with HA. Evidence shows that hemophiliacs have a lower QoL than healthy individuals and joint arthropathy plays an important role in decreasing QoL.[37,38] Joint pain in hemophilia is a predictor of disability and consequently affects the various aspects of QoL.[39] Chen *et al*.[40] suggested that recovery of ROM in large joints can be an advisable therapeutic strategy for improving QoL in hemophiliacs.[40] According to the International Classification of Functioning, Disability, and Health, changes in the body structural and functional components affect the level of activity and participation of individuals. Hence, it seems that the positive effect of PEMF on pain, ROM, and crepitus of the knee joint as a body structure led to improvement of the function of the knee, which subsequently improved gait and activity and resulted in greater participation of the individual in life situations and QoL.

Studies indicate that the effects of PEMF on knee OA are most effective at a frequency of about 50–75 Hz on cartilage protection and morphological improvement.[35,36,41] Lower frequencies (1–30 Hz) mostly improved the clinical symptoms of knee OA, including pain and stiffness.[42,43] In the current study, two frequencies were used to gain these therapeutic properties. Another strength of our study was the participation of subjects with knee joint destruction of similar severity, which made our results more reliable.

The present study had some limitations. This included a lack of follow-up after the treatment and awareness of our examiner about the groupings of patients. Further clinical trials with follow-ups and a double-blinded design can confirm PEMF effectiveness.

In addition, the use of different electromagnetic protocols may have different therapeutic effects; therefore, comparison of different intensities, wave shapes, and frequencies of PEMF in future studies could clarify the effect of these factors. Future investigations can also examine the effect of PEMF more accurately by using magnetic resonance imaging for assessing articular conditions.

Conclusions

The results of this study showed that treatment with PEMF significantly improved clinical signs, pain intensity, and QoL in hemophiliacs with moderate HA of the knee. The application of PEMF could help prevent further joint damage and prevent functional decline in patients.

Acknowledgments

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Conflicts of interest

There are no conflicts of interest.

References

1. Lobet S, Hermans C, Lambert C. Optimal management of hemophilic arthropathy and hematomas. J Blood Med 2014;5:207-18.
2. Raffini L, Manno C. Modern management of haemophilic arthropathy. Br J Haematol 2007;136:777-87.
3. Valentino LA, Hakobyan N, Rodriguez N, Hoots WK. Pathogenesis of haemophilic synovitis: Experimental studies on blood-induced joint damage. Haemophilia 2007;13 Suppl 3:10-3.
4. Rodriguez-Merchan EC, Jimenez-Yuste V, Aznar JA, Hedner U, Knobe K, Lee CA, *et al*. Joint protection in haemophilia. Haemophilia 2011;17 Suppl 2:1-23.
5. Rodriguez-Merchan EC. Musculoskeletal complications of hemophilia. HSS J 2010;6:37-42.
6. Roosendaal G, Lafeber F. Prophylactic treatment for prevention of joint disease in hemophilia--cost versus benefit. N Engl J Med 2007;357:603-5.
7. de la Corte-Rodriguez H, Rodriguez-Merchan EC. The role of physical medicine and rehabilitation in haemophiliac patients. Blood Coagul Fibrinolysis 2013;24:1-9.
8. Shupak NM, Prato FS, Thomas AW. Therapeutic uses of pulsed magnetic-field exposure: A review. Radio Sci Bull 2003;307:9À30.
9. Markov MS. Pulsed electromagnetic field therapy history, state of the art and future. Environmentalist 2007;27:465-75.
10. Markov MS. Expanding use of pulsed electromagnetic field therapies. Electromagn Biol Med 2007;26:257-74.
11. Ay S, Evcik D. The effects of pulsed electromagnetic fields in the treatment of knee osteoarthritis: A randomized, placebo-controlled trial. Rheumatol Int 2009;29:663-6.
12. van Nguyen J, Marks R. Pulsed electromagnetic fields for treating osteo-arthritis. Physiotherapy 2002;88:458-70.
13. Eid MA, Aly SM. LASER versus electromagnetic field in treatment of hemarthrosis in children with hemophilia. Lasers Med Sci 2015;30:2179-87.
14. Parhampour B, Torkaman G, Hoorfar H, Hedayati M, Ravanbod R. Effects of short-term resistance training and pulsed electromagnetic fields on bone metabolism and joint function in severe haemophilia A patients with osteoporosis: A randomized controlled trial. Clin Rehabil 2014;28:440-50.
15. Tiktinsky R, Chen L, Narayan P. Electrotherapy: Yesterday, today and tomorrow. Haemophilia 2010;16 Suppl 5:126-31.
16. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. Clin Orthop Relat Res 1980;149:153-9.
17. Jelbert A, Vaidya S, Fotiadis N. Imaging and staging of haemophilic arthropathy. Clin Radiol 2009;64:1119-28.
18. Fischer K, Poonnoose P, Dunn AL, Babyn P, Manco-Johnson MJ, David JA, *et al*. Choosing outcome assessment tools in haemophilia care and research: A multidisciplinary perspective. Haemophilia 2017;23:11-24.
19. Chesworth BM, Culham E, Tata GE, Peat M. Validation of outcome measures in patients with patellofemoral syndrome. J Orthop Sports Phys Ther 1989;10:302-8.
20. Feldman BM, Funk S, Lundin B, Doria AS, Ljung R, Blanchette V, *et al*. Musculoskeletal measurement tools from the International Prophylaxis Study Group (IPSG). Haemophilia 2008;14 Suppl 3:162-9.
21. Fischer K, de Kleijn P. Using the Haemophilia Joint Health Score for assessment of teenagers and young adults: Exploring reliability and validity. Haemophilia 2013;19:944-50.
22. Feldman BM, Funk SM, Bergstrom BM, Zourikian N, Hilliard P, van der Net J, *et al*. Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: Validity of the hemophilia joint health score. Arthritis Care Res (Hoboken) 2011;63:223-30.
23. Hilliard P, Funk S, Zourikian N, Bergstrom BM, Bradley CS, McLimont M, *et al*. Hemophilia joint health score reliability study. Haemophilia 2006;12:518-25.
24. Arranz P, Remor E, Quintana M, Villar A, Díaz JL, Moreno M, *et al*. Development of a new disease-specific quality-of-life questionnaire to adults living with haemophilia. Haemophilia 2004;10:376-82.
25. Remor E, Young NL, Von Mackensen S, Lopatina EG. Disease-specific quality-of-life measurement tools for haemophilia patients. Haemophilia 2004;10 Suppl 4:30-4.
26. Remor E, Arranz P, Quintana M, Villar A, Jiménez-Yuste V, Diaz JL, *et al*. Psychometric field study of the new haemophilia quality of life questionnaire for adults: The 'Hemofilia-QoL'. Haemophilia 2005;11:603-10.
27. Zorzi C, Dall'Oca C, Cadossi R, Setti S. Effects of pulsed electromagnetic fields on patients' recovery after arthroscopic surgery: Prospective, randomized and double-blind study. Knee Surg Sports Traumatol Arthrosc 2007;15:830-4.
28. Ganesan K, Gengadharan AC, Balachandran C, Manohar BM, Puvanakrishnan R. Low frequency pulsed electromagnetic field--a viable alternative therapy for arthritis. Indian J Exp Biol 2009;47:939-48.
29. Fini M, Giavaresi G, Torricelli P, Cavani F, Setti S, Canè V, *et al*. Pulsed electromagnetic fields reduce knee osteoarthritic lesion progression in the aged Dunkin Hartley guinea pig. J Orthop Res 2005;23:899-908.
30. Nelson FR, Zvirbulis R, Pilla AA. Non-invasive electromagnetic field therapy produces rapid and substantial pain reduction in early knee osteoarthritis: A randomized double-blind pilot study. Rheumatol Int 2013;33:2169-73.
31. Heijnen L, de Kleijn P. Physiotherapy for the treatment of articular contractures in haemophilia. Haemophilia 1999;5 Suppl 1:16-9.
32. Bagnato GL, Miceli G, Marino N, Sciortino D, Bagnato GF. Pulsed electromagnetic fields in knee osteoarthritis: a double blind, placebo-controlled, randomized clinical trial. Rheumatology (Oxford) 2016;55:755-62.
33. Thamsborg G, Florescu A, Oturai P, Fallentin E, Tritsaris K, Dissing S. Treatment of knee osteoarthritis with pulsed electromagnetic fields: A randomized, double-blind, placebo-controlled study. Osteoarthritis Cartilage 2005;13:575-81.
34. Tepper OM, Callaghan MJ, Chang EI, Galiano RD, Bhatt KA, Baharestani S, *et al*. Electromagnetic fields increase *in vitro* and *in vivo* angiogenesis through endothelial release of FGF-2. FASEB J 2004;18:1231-3.
35. Ciombor D, Aaron R, Simon B. Modification of osteoarthritis by electromagnetic field exposure. Arthritis Rheumatism 2001;44:S41.
36. Fini M, Torricelli P, Giavaresi G, Aldini NN, Cavani F, Setti S, *et al*. Effect of pulsed electromagnetic field stimulation on knee cartilage, subchondral and epyphiseal trabecular bone of aged Dunkin Hartley guinea pigs. Biomed Pharmacother 2008;62:709-15.
37. Mauser-Bunschoten EP, Fransen Van De Putte DE,

Schutgens RE. Co-morbidity in the ageing haemophilia patient: The down side of increased life expectancy. Haemophilia 2009;15:853-63.
38. Beeton K, Neal D, Lee C. An exploration of health-related quality of life in adults with haemophilia--A qualitative perspective. Haemophilia 2005;11:123-32.
39. Wallny T, Hess L, Seuser A, Zander D, Brackmann HH, Kraft CN. Pain status of patients with severe haemophilic arthropathy. Haemophilia 2001;7:453-8.
40. Chen CM, Huang KC, Chen CC, Huang SU, Huang CE, Chen YY, *et al*. The impact of joint range of motion limitations on health-related quality of life in patients with haemophilia A: A prospective study. Haemophilia 2015;21:e176-84.
41. Veronesi F, Torricelli P, Giavaresi G, Sartori M, Cavani F, Setti S, *et al*. *In vivo* effect of two different pulsed electromagnetic field frequencies on osteoarthritis. J Orthop Res 2014;32:677-85.
42. Pipitone N, Scott DL. Magnetic pulse treatment for knee osteoarthritis: A randomised, double-blind, placebo-controlled study. Curr Med Res Opin 2001;17:190-6.
43. Trock DH, Bollet AJ, Markoll R. The effect of pulsed electromagnetic fields in the treatment of osteoarthritis of the knee and cervical spine. Report of randomized, double blind, placebo controlled trials. J Rheumatol 1994;21:1903-11.