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Original Article

Pulsed electromagnetic field with or without exercise therapy in the treatment of benign prostatic hyperplasia

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Abstract. [Purpose] To investigate the effect of pulsed electromagnetic field with or without exercise therapy in the treatment of benign prostatic hyperplasia. [Subjects and Methods] Sixty male patients aged 55–65 years with benign prostatic hyperplasia were invited to participate in this study. Patients were randomly assigned to Group A (n=20; patients who received pulsed electromagnetic field in addition to pelvic floor and aerobic exercises), Group B (n=20; patients who received pulsed electromagnetic field), and Group C (n=20; patients who received placebo electromagnetic field). The assessments included post-void residual urine, urine flow rate, prostate specific antigen, white blood cells count, and International Prostate Symptom Score were weighed, before and after a 4-week intervention. [Results] There were significant differences in Group A and B in all parameters. Group C showed non-significant differences in all measured variables except for International Prostate Symptom Score. Among groups, all parameters showed highly significant differences in favor of Group A. There were non-significant differences between Group A and B and significant difference between Groups A and C and between Groups B and C. [Conclusion] The present study demonstrated that electromagnetic field had a significant impact on the treatment of benign prostatic hyperplasia. Accordingly, electromagnetic field can be utilized alone or in combination with other physiotherapy modalities. Moreover, clinicians should have the capacity to perceive the advantages accomplished using extra treatment alternatives. Electromagnetic field is a safe, noninvasive method and can be used for the treatment of benign prostatic hyperplasia.

Key words: Benign prostatic hyperplasia, Pulsed electromagnetic field, Pelvic floor exercises

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is defined as the origination of smooth muscle enlargement and proliferation of epithelial cells within the transitional area of the prostate gland. Enlargement of the gland might manifest in the lower urinary tract in two ways: (1) critical bladder outlet blocking due to enlarged tissue; and (2) increased tone of the diseased smooth muscle as well as the resistance inside the gland[1)]. Voiding dysfunction might also be an obstructive characteristic of an enlarged prostate, while overactive bladder is thought to be a prominent reason for the storage symptoms observed in the lower urinary tract[2)]. The challenges created by lower urinary tract symptoms due to enlarged prostate in elderly men might be increasing and lead to this primitive diagnosis in public health[3)].

The central plan of BPH treatment involves reducing the troublesome lower urinary tract symptoms that occur due to

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prostatic augmentation. Treatment should be adjusted as the disease progresses and getting away of complexities that can be joined with BPH[4]. Different pharmacologic groups including alpha-adrenergic blockers, 5-alphareductase suppressors, cholinergic inhibitors, and phytotherapeutics were used[5]. Determining the correct therapeutics for BPH is difficult. In the treatment of troublesome lower urinary tract symptoms, that is basic for healthcare professions as the manifestations may occur due to synergies between the pelvic organs and the central nervous system[6].

Treatment strategies also involve the surgical removal of all or part of the prostate gland, which can provoke uncontrolled urinary or sexual impediments[7]. Exercises before and after surgery can have positive impacts on restoring function, especially managing incontinence. Pelvic floor exercises deliver distinctive unmistakable effects on the prostate, particularly in individuals who present with BPH[8].

Exercise can enhance blood circulation to the pelvic region, enabling the body to actively eliminate harmful agents and waste products; decrease pressure, therefore decompressing prostatic tissue[9]; and lessen abdominal overweight, which enhances the lower body stress and consequently loosens the prostate/rectal zone, promoting blood stream toward and outside these sites[10].

The physiological impacts of low-frequency electromagnetic field (EMF) have been suggested to include the possibility of different considerations since they could enter through the body tissues. The EMF is thought to have the ability to affect the cells that induce different cellular changes including cell reproduction and differentiation[11], programmed cell death, new DNA formation, RNA synthesis, protein formulation, protein phosphorylation, redox-mediated increases in inflammatory cells, increased microvesicular motility, ATP production, hormone secretion, increased antioxidant activity of enzymes, enhanced cellular metabolic action, and hindered adherence activity[12]. The organization of restraining action and signal augmentation on organic activity has earlier been speculated to be induced only through biochemical carriers and receptors; however, present studies prove that molecular synergies may not remain the unique determinants implicated in the biological interface. Chemical agents are possibly the particle ingredients accentuated by directing energy fields carrying signal transduction[13]. EMF possesses numerous well-reported biological effects including inflammation and pain suppression. This therapy is noninvasive, secure, and easy to use for treating the origin of discomfort, damage, and inflammation[14]. Actually, there were limited number of studies conducted that investigated the effects of EMF in the treatment of BPH. Furthermore, the present study adds exercises therapy in the form of pelvic floor and aerobic exercises. Therefore, this study aimed to investigate the effect of pulsed EMF with or without exercise therapy in the treatment of BPH.

SUBJECTS AND METHODS

This randomized clinical study was performed according to rules, guidelines, and measures for research concerning humans, and written informed consent was obtained from each participant. The patients participated voluntarily without monetary compensation and the study was performed in agreement with the human rights legislation from the Declaration of Helsinki (1979). The data obtained were gathered between April and October 2016 in Cairo University Hospitals, Department of Urology, Cairo, Egypt.

A total of 60 male patients were invited to join the study; the inclusion criteria were: age 55–65 years; diagnosis of BPH; prostate specific antigen (PSA)<4 ng/ml; no clear abnormalities on urological examination; and the ability to communicate, comprehend, and agree to the study protocol. The exclusion criteria included symptoms for <6 months, acute or chronic urethritis, urinary stones, bacterial or inflammatory chronic prostatitis or chronic pelvic pain syndrome, bladder cancer, urethral strictures, neurogenic bladder dysfunction, restricted mobility, and antimicrobial or anti-inflammatory medication up to 4 weeks before study enrollment.

Study design: Double-blind controlled randomized comparative study. Each subject underwent the same evaluation that was performed by the same therapist at the beginning and end of the study (after 4 weeks). All subjects were asked to maintain their activity levels during the study period to exclude the personal variations of the results.

After the baseline evaluation, patients were randomly assigned to Group A (n=20; patients who received pulsed EMF in addition to pelvic floor and aerobic exercises), Group B (n=20; patients who received only PEMF), or Group C (n=20; patients who received placebo PEMF).

A DANTIC UD 5000/5500 Urodynamic examination system was utilized to perform the urodynamic investigation and measure post-void residual urine and urine flow rate for each patient pre- and post-treatment. Also, the prostate specific antigen (PSA), white blood cell (WBCs) count, and International Prostate Symptom Score (IPSS) were assessed before and after a 4-week intervention.

An EMF device (PMT-120 Desktop, ElectroMeds, USA) was worked with impact to patient with damped trains of magnetic oscillations with a period of 20–1,100 nanoseconds and an intensity of 0.12–18 microtesla and a decreased damping of at least 0.05 and a repetition rate between the trains in the range of 25–30 Hz. The application was directed to the perineum with the patient lying in the lateral recumbent position. The treatment was conducted for 30 minutes for each day, five times each week for 4 progressive weeks.

After the treatment protocol achievement (4 weeks of treatment), patients were re-assessed using total PSA, complete blood count values, post-void residual urine, estimated urine flow rate, and IPSS.

Aerobic exercises: regular aerobic exercise for 20–60 minutes undertaken five times each week at 55–90% of the maximal

Table 1. The demographic data and the clinical baseline measurements of the three groups

	Group (A)	Group (B)	Group (C)
Age (years)	65.2 ± 4.0	63.8 ± 4.6	64.0 ± 4.8
Weight (kg)	72.0 ± 4.3	71.0 ± 4.4	70.0 ± 3.9
Height (cm)	174.0 ± 2.3	172.0 ± 4.9	172.7 ± 4.4
BMI (kg/ m^2)	23.7 ± 1.2	24.0 ± 1.7	23.7 ± 1.7

Data represent the mean ± standard deviation, BMI: body mass index

Table 2. Values of the variables assessed before and after intervention

	Group A (n=20)		Group B (n=20)		Group C (n=20)	
	Pre	Post	Pre	Post	Pre	Post
RU	93.0 ± 11.7	68.0 ± 12.8*	98.0 ± 11.5	71.5 ± 12.6*	97.5 ± 11.6	95.5 ± 10.9
FR	13.0 ± 3.0	17.2 ± 2.3*	11.3 ± 2.6	17.4 ± 2.3*	12.0 ± 3.0	12.2 ± 3.3
PSA	3.0 ± 0.5	2.6 ± 0.5*	2.9 ± 0.5	2.5 ± 0.6*	3.1 ± 0.4	3.0 ± 0.5
WBC	4.8 ± 0.7	3.9 ± 0.4*	5.0 ± 0.8	4.1 ± 0.7*	4.7 ± 0.6	4.7 ± 0.6
IPSS	22.0 ± 2.3	15.5 ± 2.3*	20.6 ± 2.1	15.2 ± 2.3*	20.8 ± 1.7	20.2 ± 2.0*

Data represent the mean ± standard deviation. RU: post void residual urine volume, FR: urine flow rate, PSA: P values represent tests between the group A vs. group B, group A vs. group C and group B vs. group C. *p<0.05 statistically significant difference within the group pre and post the intervention.

heart rate is estimated as 220 −age in years. Aerobic exercises consist of moderate effort walking very briskly (4 mph) and bicycling with light exertion (10–12 mph) in addition to strenuous exercises consisting of jogging at 6 mph and bicycling quickly (14–16 mph) and flexibility exercises for major muscles consisting of two to four sets of each exercise two to three times each week.

Pelvic floor exercises: The patients were instructed to empty their bladders before the treatment sessions in an effort to feel comfortable and relaxed during the treatment session. Each patient was prepared and taught a program of pelvic floor exercises to be performed in daily sessions in lying, sitting, and standing positions consisting of 10 seconds of contractions followed by 10 seconds of relaxation and repeating the exercises 15 times each session. The contraction and relaxation times were continuously expanded by 1 second every week as a training for the slow twitch muscle fibers. While, fast twitch muscle fibers can be trained through asking the patient to contract as if he controls his urine by quick contraction and relaxation of the levator ani muscles 20 times, rest for ten seconds, and then repeat again for a total of 2 to 4 "sets" of contractions.

Descriptive statistics are presented as mean and standard deviation (SD). A paired t-test was used to compare intergroup mean age, weight, height, and body mass index before the treatment protocol. It was also used to compare intra- and inter-group WBC count, PSA, post-void residual urine, urine flow rate, and IPSS values. Analysis of variance (ANOVA) was used to compare groups with Bonferroni's post hoc test. A significance level of 0.05 was used throughout all statistical tests within the study; p values<0.05 were considered significant. The smaller the obtained p value, the more significant the outcomes.

RESULTS

This study included 67 patients with BPH and a PSA<4 ng/ml without clear abnormalities on a urological examination. Of those 67 patients, seven did not meet the inclusion criteria and were excluded from the study due to various causes: unwilling to participate (n=3), insufficient number of evaluation values (n=2), refusal to continue the treatment protocol (n=1), and not completing two sessions of the assigned intervention (n=1). As such, the final sample consisted of 60 patients, 20 in each group. The demographic data for the three groups were tested pre-intervention to confirm homogeneity, and no significant difference was found (p>0.05) (Table 1).

The results showed no significant differences in the baseline values of post-void residual urine (F=1.12, p=0.33), urine flow rate (F=1.69, p=0.19), total PSA (F=0.36, p=0.70), WBCs (F=1.19, p=0.31), and IPSS (F=2.64, p=0.08) among the three groups (Table 2).

Intragroup comparisons showed a significant difference (p<0.05) in Groups A and B in all parameters, while Group C showed non-significant differences (p>0.05) in all measured variables except for IPSS (Table 2). Intergroup post-intervention comparisons revealed by ANOVA that all parameters differed significantly among groups in favor of Group A as follows: RU (F=11.91, p=0.0001), FR (F=24.11, p=0.0001), PSA (F=51.04, p=0.001), WBCs (F=7.93, p=0.001), and IPSS (F=31.77, p=0.0001).

Regarding the post hoc analysis, there was a non-significant difference (p>0.05) between Groups A and B, while there

Table 3. The symptom scores and free uroflowmetry for the three groups before and after treatment

	G (A) vs. G (B)	G (A) vs. G (C)	G (B) vs. G (C)
	MD	MD	MD
Ru	−3.50	−19.50*	−16.00*
FR	−0.22	5.05*	5.27*
PSA	0.07	−0.45*	−0.53*
WBC	−0.15	−0.76*	−0.61*
IPSS	0.30	−4.75*	−5.05*

GA: group A, GB: group B, GC: group C, MD: main difference. *p<0.05 statistically significant difference.

were significant differences ($p<0.05$) between Groups A and C and between Groups B and C (Table 3).

DISCUSSION

The results of the current study demonstrated that the use of PEMF and exercise therapy is beneficial in the treatment of BPH. This was presented as a significant reduction in WBCs count, PSA antigen, IPSS, and post-void residual urine in addition to the significantly increased urine flow rate in Groups A and B, while Group C showed non-significant changes in values except for IPSS, which may be due to the improved frequency, urgency, and nectoria. Studies to date have explained that the mechanisms through which PEMF acts are complex and reasonably include several pathways[15)]. Further considerations are required to ascertain the principles for these impacts in BPH. The anti-inflammatory capacity of PEMF should additionally be granted[16)]. Inflammation of the prostate gland might signify a powerful factor in determining prostatic swelling and improving symptoms. Prostatic inflammation may express a mechanism of hyperplastic transformations to befall[11)]. Plenty of growth agents and cytokines contribute to the inflammatory process of the prostate. The highest PEMF potential was displayed in its capacity to enhance the effects of inflammation by reducing inflammatory cytokines and improving cellular metabolism[17)]. Consequently, by diminishing the inflammatory processes, PEMF may possess the ability to overcome developments related to BPH and its associated symptoms[18)]. A study in 2011 of 20 humans showed that the clinical manifestations of BPH were significantly diminished following PEMF administration, so the influence persisted for 12 months[19)]. Additional clinical studies could present further data covering the efficiency of this approach in the same category of patients.

Electromagnetic treatments are dependent upon the time-varying EMF habitually created at low wavelengths through an alternative current reaching through a coil[20)]. The fundamental discrepancy with other direct fields is that time-varying magnetic fields might produce magnetic fields with notable energy in the body; furthermore, its amount could be determined using electrical laws such as Faraday's equation. Static EMF possesses no auxiliary electric fields and cannot transport magnetic power to the movable energized particles[21)], designating the efficiency of that type of therapy and describing the deficiency of strong medical sign in the systematic research to encourage its application. PEMF is a broad approach employed in the treatment of various medical dysfunctions, such as musculoskeletal disorders[22)], neurological manifestations[23, 24)], and urological disciplines[25)]. The mechanism of the beneficial performance of the PEMF upon living organisms is not completely obvious yet; however, clinical studies have reported its convenient role in decreasing inflammation, forming new blood vessels, and relieving pain[26)]. Plenty of clinical studies have recommended that magnetic field stimulating properties can hasten organ healing[27)]. Its application on the prostate gland helps reduce postoperative problems and was observed to excite the prostate gland and promote blood flow[28)], demonstrating a definite impact on revascularization and the circulatory consequences of the prostate[29)].

Several explanations have been suggested to describe how physical exercises decrease BPH hazards. Androgens remain engaged in the development and sustaining of BPH, and those who joined the continued endurance disciplines possess, as a group, lower resting testosterone values[30)]. They attributed their decisions to diminished sympathetic nervous action rather than decreased prostate mass since the exercises were greatly relevant to characteristic BPH than prostatic augmentation[31)].

Some studies imply that physical exercises decrease the probability of BPH; however, the exercise is simply of low to medium intensity (ascending stairs, hiking, rowing, or gymnastics)[32)]. This information is valuable since rare studies have stated that this advantage was correlated with different health results such as cardiovascular disorders.

The limitation of the current study was its small sample size, which might affect its results; therefore, it is advisable to increase the number of participants in future studies to obtain much better results. Furthermore, the addition of other investigations and study groups can support our results.

PEMF seems, by all accounts, to be a promising treatment method and appears to exert valuable consequences in the management of BPH. Additional studies are most likely required to clarify the correct mechanism through which EMF impacts BPH and present it as a safe and noninvasive technique in the treatment of prostate injuries.

Conflict of interests

The authors declare that they have no competing interests.

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REFERENCES

1) Reynard JM: Does anticholinergic medication have a role for men with lower urinary tract symptoms/benign prostatic hyperplasia either alone or in combination with other agents? Curr Opin Urol, 2004, 14: 13–16. [Medline] [CrossRef]
2) Di Silverio F, Gentile V, Pastore AL, et al.: Benign prostatic hyperplasia: what about a campaign for prevention? Urol Int, 2004, 72: 179–188. [Medline] [CrossRef]
3) O'Leary MP: Lower urinary tract symptoms/benign prostatic hyperplasia: maintaining symptom control and reducing complications. Urology, 2003, 62: 15–23. [Medline] [CrossRef]
4) Male lower urinary tract dysfunction: evaluation and management. In: 6th International Consultation on New Developments in Prostate Cancer and Prostate Diseases. McConnell J, Abrams P, Denis L et al. (eds.), Paris: Health Publications, 2006.
5) Abrams P, Chapple C, Khoury S, et al. International Scientific Committee: Evaluation and treatment of lower urinary tract symptoms in older men. J Urol, 2009, 181: 1779–1787. [Medline] [CrossRef]
6) Fourcade RO, Lacoin F, Rouprêt M, et al.: Outcomes and general health-related quality of life among patients medically treated in general daily practice for lower urinary tract symptoms due to benign prostatic hyperplasia. World J Urol, 2012, 30: 419–426. [Medline] [CrossRef]
7) Gacci M, Ficarra V, Sebastianelli A, et al.: Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis. J Sex Med, 2014, 11: 1554–1566. [Medline] [CrossRef]
8) Patel AV, Rodriguez C, Jacobs EJ, et al.: Recreational physical activity and risk of prostate cancer in a large cohort of U.S. men. Cancer Epidemiol Biomarkers Prev, 2005, 14: 275–279. [Medline] [CrossRef]
9) Kenfield SA, Stampfer MJ, Giovannucci E, et al.: Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J Clin Oncol, 2011, 29: 726–732. [Medline] [CrossRef]
10) Galvão DA, Taaffe DR, Spry N, et al.: Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol, 2010, 28: 340–347. [Medline] [CrossRef]
11) McFarlane JP, Foley SJ, de Winter P, et al.: Acute suppression of idiopathic detrusor instability with magnetic stimulation of the sacral nerve roots. Br J Urol, 1997, 80: 734–741. [Medline] [CrossRef]
12) Salvatore JR, Weitberg AB, Mehta S: Nonionizing electromagnetic fields and cancer: a review. Oncology (Williston Park), 1996, 10: 563–570, discussion 573–574, 577–578. [Medline]
13) Binhi V, Savin A: Effects of weak magnetic fields on biological systems: physical aspects. Phys Uspekhi, 2003, 46: 259–291. [CrossRef]
14) Haddad JB, Obolensky AG, Shinnick P: The biologic effects and the therapeutic mechanism of action of electric and electromagnetic field stimulation on bone and cartilage: new findings and a review of earlier work. J Altern Complement Med, 2007, 13: 485–490. [Medline] [CrossRef]
15) Mayer-Wagner S, Passberger A, Sievers B, et al.: Effects of low frequency electromagnetic fields on the chondrogenic differentiation of human mesenchymal stem cells. Bioelectromagnetics, 2011, 32: 283–290. [Medline] [CrossRef]
16) Bersani F, Marinelli F, Ognibene A, et al.: Intramembrane protein distribution in cell cultures is affected by 50 Hz pulsed magnetic fields. Bioelectromagnetics, 1997, 18: 463–469. [Medline] [CrossRef]
17) Neĭmark AI, Snegirev IV, Neĭmark BA: [Transrectal magnetotherapy of the prostate from Intramag device in prophylaxis of postoperative complications of transurethral resection of prostatic adenoma]. Urologiia, 2006, 75: 75, 77–79. [Medline]
18) Rohde C, Chiang A, Adipoju O, et al.: Effects of pulsed electromagnetic fields on interleukin-1 beta and postoperative pain: a double-blind, placebo-controlled, pilot study in breast reduction patients. Plast Reconstr Surg, 2010, 125: 1620–1629. [Medline] [CrossRef]
19) Giannakopoulos XK, Giotis C, Karkabounas SC, et al.: Effects of pulsed electromagnetic fields on benign prostate hyperplasia. Int Urol Nephrol, 2011, 43: 955–960. [Medline] [CrossRef]
20) Kawczyk-Krupka A, Sieron A, Shani J, et al.: Biological effects of extremely low-frequency magnetic fields on stumlated macrophages J774-2 in cell culture. Electromagn Biol Med, 2002, 21: 141–153. [CrossRef]
21) Tenuzzo B, Chionna A, Panzarini E, et al.: Biological effects of 6 mT static magnetic fields: a comparative study in different cell types. Bioelectromagnetics, 2006, 27: 560–577. [Medline] [CrossRef]
22) Trock DH: Electromagnetic fields and magnets. Investigational treatment for musculoskeletal disorders. Rheum Dis Clin North Am, 2000, 26: 51–62, viii. [Medline] [CrossRef]
23) Raji AM: An experimental study of the effects of pulsed electromagnetic field (Diapulse) on nerve repair. J Hand Surg [Br], 1984, 9: 105–112.[Medline] [CrossRef]
24) Kamel DM, Hamed NS, Abdel Raoof NA, et al.: Pulsed magnetic field versus ultrasound in the treatment of postnatal carpal tunnel syndrome: A randomized controlled trial in the women of an Egyptian population. J Adv Res, 2017, 8: 45–53.[Medline] [CrossRef]
25) Tokalov SV, Gutzeit HO: Weak electromagnetic fields (50 Hz) elicit a stress response in human cells. Environ Res, 2004, 94: 145–151. [Medline] [CrossRef]
26) Túnez I, Drucker-Colín R, Jimena I, et al.: Transcranial magnetic stimulation attenuates cell loss and oxidative damage in the striatum induced in the 3-nitro-

propionic model of Huntington’s disease. J Neurochem, 2006, 97: 619–630. [Medline] [CrossRef]

27) Vianale G, Reale M, Amerio P, et al.: Extremely low frequency electromagnetic field enhances human keratinocyte cell growth and decreases proinflammatory chemokine production. Br J Dermatol, 2008, 158: 1189–1196. [Medline] [CrossRef]

28) Anninos P, Papadopoulos I, Kotini A, et al.: Differential diagnosis of prostate lesions with the use of biomagnetic measurements and non-linear analysis. Urol Res, 2003, 31: 32–36. [Medline]

29) Johnson MT, Waite LR, Nindl G: Noninvasive treatment of inflammation using electromagnetic fields: current and emerging therapeutic potential. Biomed Sci Instrum, 2004, 40: 469–474. [Medline]

30) Dal Maso L, Zucchetto A, Tavani A, et al.: Lifetime occupational and recreational physical activity and risk of benign prostatic hyperplasia. Int J Cancer, 2006, 118: 2632–2635. [Medline] [CrossRef]

31) Rohrmann S, Crespo CJ, Weber JR, et al.: Association of cigarette smoking, alcohol consumption and physical activity with lower urinary tract symptoms in older American men: findings from the third National Health And Nutrition Examination Survey. BJU Int, 2005, 96: 77–82. [Medline] [CrossRef]

32) Williams PT: Effects of running distance and performance on incident benign prostatic hyperplasia. Med Sci Sports Exerc, 2008, 40: 1733–1739. [Medline] [CrossRef]