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Radial Extracorporeal Shock Wave Therapy as a Novel Agent for Benign Prostatic Hyperplasia Refractory to Current Medical Therapy

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Abstract

This study aimed to assess efficacy and safety data from pilot trials of the radial extracorporeal shock wave therapy (rESWT) to treat benign prostatic hyperplasia (BPH) refractory to current medical therapy. A total of 29 men with lower urinary tract symptoms (LUTS) suggestive of BPH who had responded poorly to medical therapy for at least 6 months and were poor surgical candidates were enrolled. Each participant was treated with rESWT once a week for 8 weeks, each by 2000 impulses at 2.0 bar and 10 hertz of frequency. International Prostate Symptom Score (IPSS), quality of life (QoL), and International Index of Erectile Function-5 (IIEF-5) were evaluated before treatment, after the fourth and eighth rESWT, and 3 months after the end of treatment. Peak urinary flow (Q_{max}) and postvoid residual (PVR) were assessed. Safety was also documented. Statistically significant clinical improvements were reported for IPSS, QoL, and IIEF-5 after treatment, and those were sustained until 3 months follow-up. Q_{max} and PVR improved evidently at 8 weeks with a 63% and 70% improvement, respectively. The only adverse event was the occasional perineum pain or discomfort, which usually disappeared within 3 days. The rESWT may be an effective, safe, and noninvasive treatment for symptomatic BPH in selected patients whose medical treatment has faced failure and are poor surgical candidates.

Keywords

benign prostatic hyperplasia, radial extracorporeal shock wave therapy, poor surgical candidate

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Clinical benign prostatic hyperplasia (BPH) is one of the most common diseases in aging men which can lead to lower urinary tract symptoms (LUTS). The incidence of BPH rises markedly with increased age. Autopsy studies have observed a histological prevalence of 8%, 50%, and 80% in the fourth, sixth, and ninth decades of life, respectively (Lim, 2017). BPH has already affected the health physically and emotionally, associated with great disease burden.

Multiple treatment modalities for BPH have arisen, including lifestyle modifications, α-blockers (α_1-adrenoceptor antagonists), 5α-reductase inhibitors, phytochemicals, and BPH-related surgery (Homma et al., 2017). Pharmacotherapy is usually indicated for BPH, but many patients have inadequate efficacy, not to mention side effects such as sexual dysfunction, urinary retention, and orthostatic hypotension (Homma et al., 2017). Surgery is indicated for persistent LUTS despite conservative therapies, or BPH-related comorbidities, such as urinary retention (Homma et al., 2017). The surgical approaches and less invasive procedures have varying degrees of side effects and complications, such as

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ejaculatory dysfunction, erectile dysfunction (ED), urethral strictures, and urinary incontinence (Homma et al., 2017; Teo, Lee, & Ho, 2017). Thus, exploration of a more effective and safe treatment strategy for BPH is a significant challenge for clinicians, and physical therapy is getting more and more attention in functional urology (Wang, Cheng, & Chuang, 2017).

Extracorporeal shock wave therapy (ESWT) was first successfully applied for lithotripsy in urology. At lower energy levels, however, shock waves have enhanced expression of vascular endothelial growth factor, endothelial nitric oxide synthase, proliferating cell nuclear antigen, chemoattractant factors, and recruitment of progenitor cells (Wang et al., 2017). ESWT has been reported as useful in musculoskeletal disorders, including muscle hypertonia, capsular fibrosis, and calcific tendinitis, through the mechanisms of neovascularization, anti-inflammation, and tissue regeneration (Akinoglu & Kose, 2018; Amelio & Manganotti, 2010; Fioramonti et al., 2012; Fischer et al., 2015; Guo et al., 2017; Heine, Prantl, & Eisenmann-Klein, 2013; Santamato et al., 2014). As a new generation of ESWT, radial ESWT (rESWT) generates the pressure wave that propagates into the body as a spherical wave (Wang et al., 2017). Unlike the focused ESWT (fESWT) waveform focus to a point, rESWT works more evenly during probe movement. rESWT is a general method with comparable results for superficial musculoskeletal disorders (Lohrer, Nauck, Korakakis, & Malliaropoulos, 2016). For the last decade, fESWT was identified to be applicable by perineal approach almost without side effects, achieving significant improvement of chronic pelvic pain syndrome-related symptoms, concerning voiding conditions (Vahdatpour et al., 2013; Zimmermann et al., 2008; Zimmermann, Cumpanas, Miclea, & Janetschek, 2009), and by penis approach to improving ED (Abu-Ghanem, Kitrey, Gruenwald, Appel, & Vardi, 2014; Gruenwald, Appel, Kitrey, & Vardi, 2013; Vardi, Appel, Kilchevsky, & Gruenwald, 2012). While, there has been no available data to address the impact of fESWT or rESWT in the setting of BHP.

For the steric structure of the prostate, the scope of action of rESWT is more extensive and diffuse than that of fESWT. So, it is speculated that rESWT might be more effective than fESWT for BPH. Based on the above researches, this study tested the hypothesis that rESWT could offer benefit in improving LUTS, erectile function, and quality of life (QoL) for the patients suffering from BHP.

Material and Method

From January 2016 to December 2017, 29 men with LUTS due to BPH were enrolled in this clinical trial study. All participants poorly responded to medical therapy with one of the α-blockers with or without finasteride for at least 6 months, were poor candidates for surgical intervention due to comorbidities, or were not interested in surgery (Hamidi Madani et al., 2013). The Ethics Committee of the Chinese registered clinical trial approved this study. The Clinical Trial Registry Number is ChiCTR-IPR-15007432. All participants were required to sign an informed consent before participation in the study. Inclusion criteria included: age $\geq$40 years; International Prostate Symptom Score (IPSS) $\geq$15; maximum flow rate (Q_{max}) $\leq$15 ml/s, postvoid residual (PVR) $<$ 300 ml; and prostate volume 25–100 ml (Dixon et al., 2015; Kim, Han, Sung, Choo, & Lee, 2014). Principal exclusion criteria were a disease that causes LUTS (urinary tract stone, urethral stricture, urinary tract infection, primary renal disease, neurogenic bladder, prostatitis); a history of prostate cancer, bladder cancer, previous prostate or urethral surgery; use of α-blockers, anticholinergics, or 5α-reductase inhibitors in the last 2 weeks; serum prostate-specific antigen (PSA) level $\geq$10 mg/L, acute urinary retention, local acute thrombosis, coagulation disorders, or taking an anticoagulant. The BPH medications and other related treatments were prohibited for the duration of the study.

The participants received the perineally applied rESWT once a week for 8 weeks. Each time 2000 pulses, with 2.0 bar and 10 hertz of frequency were delivered by R15 (diameter 15 mm) transmitter. According to preliminary tests, most patients can tolerate strengths up to 2.0 bar, and this treatment interval was selected regarding the parameters of perineal ESWT for prostatitis (Zhang, Zhang, Yu, & Ma, 2018). The device used for the study was a standard ballistic shock wave device with a radial shock wave source (MASTERPULS® MP100, STORZ MEDICAL AG, Switzerland). The instrument is operated by a skilled physiotherapist. The participants were asked to empty the bladder before the procedure and lie in lithotomic position. A standard commercial gel generally used for sonography was applied to the perineum. No anesthesia or sedation is required during the treatment.

The follow-up assessments were done at the initiation, after the fourth and eighth rESWT, and 3 months after the end of treatment. IPSS, QOL, and International Index of Erectile Function (IIEF-5) were evaluated at each time point (Homma et al., 2017). Q_{max}, PVR, and urinalysis were done before treatment and at weeks 4 and 8. Transrectal prostate volume assessment ultrasounds were done before and after the end of treatment. Adverse events were documented.

Statistical Analysis

Data analyses were performed using SPSS version 19.0 (SPSS, Chicago, IL, USA). Descriptive statistics were used for baseline and follow-up study parameters. Data

Table 1. Baseline Participant Characteristics.

Variable	Mean (*SD*)
Age, years	57 (10.4)
PSA, ng/ml	4.6 (2.1)
TRUS volume, ml	35.9 (13.8)
IPSS	28.1 (5.2)
QoL score	4.7 (1)
Q_{max}, ml/s	10.2 (5.1)
PVR, ml	114.2 (71.4)
IIEF-5	11.9 (4.1)

Note. PSA = prostate specific antigen; TRUS = transrectal ultrasound; IPSS = International Prostate Symptom Score; QoL = quality of life; Q_{max} = maximum flow rate; PVR = postvoid residual urine; IIEF-5 = International Index of Erectile Function.

are presented as mean ± standard deviation, means, and 95% confidence intervals. For efficacy outcome, a paired *t*-test was used to evaluate the change from baseline for each measure. A p value $<.05$ indicated statistical significance.

Result

Twenty-nine consented men were enrolled. Baseline participant characteristics are presented in Table 1. The 8-week-long rESWT was completed without complications, and the slight perineum pain or discomfort occasionally caused by rESWT usually disappeared within 3 days. Some participants were pleased to say that urination was smoother and urine waiting symptoms improved immediately after or the next day of rESWT. The immediate effect is not primary, so it is not assessed. Urine routine white blood cells and red blood cells did not increase abnormally after the therapy cycle. None of the participants developed urinary retention during the study. Two (7%) participants were lost to follow-up. Participants without sexual life do not apply to IIEF-5 scores.

Efficacy outcomes are presented in Tables 2 and 3. The principal measure of clinical success was the change in IPSS from baseline, and statistically significant reductions were noted at 4 weeks and maintained through the 3-month follow-up ($p < .001$) with an improvement of −10.7 (38%). QoL and IIEF scores also improved significantly from 4 weeks through the 3-month follow-up ($p < .001$) with an improvement of −2.6 (56%) and +8.7 (73%), respectively. Significant increases were reported in Q_{max} and PVR from 4 weeks to 8 weeks ($p < .001$) with an improvement of +6.0 (63%) and −80.1 (70%), respectively. The percentage of patients who moved from an obstructed Q_{max} to unobstructed voiding ($Q_{max} > 15$) is 48.3% (14/29). The prostate volume did not change significantly (before treatment: 35.8 ± 13.8 ml; after treatment: 38.8 ± 15.3 ml).

Discussion

This study showed that the 8 weeks of rESWT was well tolerated and offered continuous improvement in clinical outcomes of BPH participants from 4 weeks to 8 weeks, and that was sustained until 3 months follow-up. The only adverse event was the slight perineum pain or discomfort occasionally caused by rESWT, which usually disappeared within 3 days. Unlike other therapies that may cause side effects of sexual dysfunction, the IIEF of the treated men with ED significantly improved at 4 weeks and remained increased at the 3-month follow-up. There is almost no literature on rESWT of BPH.

BPH is an enlargement of the prostate gland due to progressive hyperplasia of the stromal and glandular cells, including smooth muscle and epithelial cell, as well as collagen fibrils proliferation and calcification in the prostate transition zone. It is reported that smooth muscle spasm is a potential pathological mechanism of LUTS caused by BHP (Homma et al., 2017). Treatment with α-blockers may be helpful, but side effects such as fatigue, dizziness, headache and postural hypotension may preclude the use of these agents in the elderly, especially in those treated with other antihypertensive medications (Homma et al., 2017). Medical therapy with a 5α-reductase inhibitor requires a longer duration of treatment to reach the maximal effect (Homma et al., 2017).

It is speculated that most of the effects of rESWT on alleviating LUTS are based on its antispasmodic mechanism. There are reductions in muscle tone and spasticity after applying ESWT in patients with upper arm hypertonia and hypertonic plantar flexor muscles caused by a stroke (Amelio & Manganotti, 2010; Guo et al., 2017; Santamato et al., 2014). The mechanism of ESWT has been reported to be related to the synthesis of nonenzymatic (Hatanaka et al., 2016) and enzymatic nitric oxide (Assaly-Kaddoum et al., 2016; Huang et al., 2016). Increasing evidence indicates that nitric oxide (NO) is involved in modulating the prostatic smooth muscle relaxation, in the control of the urethral outlet activity, and in the noradrenergic, noncholinergic-mediated cascades that control lower urinary tract storage and emptying (Monica & Antunes, 2018; Monica, Bian, & Murad, 2016).

Indeed, ESWT are also applied for antifibrosis, loosening adhesions, and even dissipating calcification. Experimental and clinical studies have proved the effectiveness of ESWT to the management of pathologic scar and capsular fibrosis by degrading fibrotic tissue, which was accompanied by synergistic alterations in pro- and antifibrotic proteins (transforming growth factor β1 and matrix metalloproteinase 2, respectively; Fioramonti et al., 2012; Fischer et al., 2015; Heine et al., 2013). ESWT also ameliorates myocardial fibrosis after acute myocardial infarction in pigs, which is associated with

Table 2. Efficacy Outcome of IPSS, QoL, and IIEF-5.

Variable	4 weeks	8 weeks	3 months
IPSS			
n (paired values)	29	29	27
Baseline	28.1 (5.2)	28.1 (5.2)	28.1 (5.4)
Follow-up	21.0 (5.1)	16.7 (5.0)	17.4 (5.1)
Change	−7.1 (3.7)	−11.4 (4.2)	−10.7 (4.6)
Mean % change (95% CI)	−25 [−30, −20]	−41 [−46, −35]	−38 [−44, −31]
p value (vs. baseline)	<.001	<.001	<.001
p value (vs. 4 weeks)	–	<.001	–
QoL			
n (paired values)	29	29	27
Baseline	4.7 (1)	4.7 (1)	4.7 (1)
Follow-up	3.0 (0.9)	2.1 (0.7)	2.1 (0.8)
Change	−1.7 (1.0)	−2.6 (0.9)	−2.6 (1.0)
Mean % change (95% CI)	−36 [−44, −27]	−56 [−63, −48]	−56 [−64, −47]
p value (vs. baseline)	<.001	<.001	<.001
p value (vs. 4 weeks)	–	<.001	–
IIEF-5			
n (paired values)	15	15	15
Baseline	11.9 (4.1)	11.9 (4.1)	11.9 (4.1)
Follow-up	16.9 (3.6)	20.5 (2.6)	20.5 (1.8)
Change	5.0 (4.2)	8.7 (4.0)	8.7 (4.0)
Mean % change (95% CI)	42 [23, 61]	73 [55, 91]	73 [55, 91]
p value (vs. baseline)	<.001	<.001	<.001
p value (vs. 4 weeks)	–	<.001	–

Note. IPSS = International Prostate Symptom Score; QoL = quality of life; IIEF = International Index of Erectile Function.

Table 3. Efficacy Outcome of Q_{max} and PVR.

Variable	Baseline	4 weeks	8 weeks
Q_{max} (ml/s)	9.7 (4.4)	12.7 (4.9)	15.7 (5.1)
Change		3.0 (1.0)	6.0 (2.4)
Mean % change (95% CI)		31 [27, 35]	63 [53, 72]
p value (vs. baseline)		<.001	<.001
p value (vs. 4 weeks)		–	<.001
PVR (ml)	114.2 (71.4)	81.7 (56.7)	34.1 (27.8)
Change		32.6 (28.3)	80.1 (55.9)
Mean % change (95% CI)		−29 [−38, −19]	−70 [−89, −51]
p value (vs. baseline)		<.001	<.001
p value (vs. 4 weeks)		–	<.001

Note. Q_{max} = maximum flow rate; PVR = postvoid residual urine.

the decreased amount of fibrocytes (Lei et al., 2013). A recent study indicated that an individualized rESWT protocol with a mean of 7 ± 1.5 sessions resulted in a high success rate with low number of recurrences for symptomatic calcific shoulder tendinopathy (Malliaropoulos et al., 2017). All of the studies above indicated a potential for rESWT to influence the proliferation and calcification process of prostatic tissue and restore its elasticity. In this study, the patient's symptoms improved rapidly, and the prostate volume did not decrease significantly. It may be because the antispasmodic effect of rESWT has a fast onset, while the antifibrosis and anticalcification effects may take a longer course of treatment, when the prostate may undergo structural changes.

For BPH, there is currently no effective noninvasive treatment other than medical treatment. Because there is no previous literature on shock wave treatment of BPH, the results of some minimally invasive procedures for

drug-refractory BPH are briefly listed. Hamidi Madani et al. (2013) conducted a survey of intraprostatic injection of BoNT-A on BPH refractory to current medical therapy. IPSS was decreased from 24.50 ± 3.83 to 13.40 ± 2.67. Q_{max} increased significantly from 7.87 ± 2.01 ml/s to 16.19 ± 1.76 ml/s, while PVR decreased from 75.60 ml to 63.50 ml insignificantly (Hamidi Madani et al., 2013). In the study of Dixon et al. (2015), they used the less invasive treatment of Rezūm System water vapor and the IPSS showed a reduction from 21.7 to 8.3. Q_{max} showed an increase from 8.1 ± 3.2 ml/s to 12.8 ± 6.4 ml/s and the decrease of PVR from 89.5 ml to 59.6 ml. Urinary retention, dysuria, and urinary urgency are the common adverse events. The results of this study are similar and almost have no side effects. The mean IPSS was decreased from 28.1 ± 5.2 to 16.7 ± 5.0 significantly. The objective parameter of Q_{max} was increased from 9.7 ± 4.4 to 15.7 ± 5.1 ml/s, and the mean PVR was decreased from 114.2 ± 71.4 ml to 34.1 ± 27.8 ml. An improvement both in the subjective parameter (IPSS) and objective parameter (Q_{max}, PVR) after treatment indicates that the noninvasive rESWT could be effective on the relief of BPH symptoms including voiding. These effects may be related to the reduction of smooth muscle tension and antifibrosis effect.

The lack of side effects within a certain dose range specific to the rESWT means that it would be possible to extend the curing cycle according to the patients' condition. No hematuria or other abnormal changes in urine routine appeared after rESWT in this study. Besides, perineal ESWT was regarded as a safe option in treating chronic pelvic pain syndrome, as PSA showed only slight or entirely absent fluctuations before and after the procedure, a further indicator that there is no reason to expect any relevant tissue damage (Zimmermann et al., 2008). Unlike current surgery and medication, rESWT is noninvasive green physiotherapy. Patients are easy to adhere to the therapy because of the continuously visible curative effect. Different from other daily physical therapy, rESWT needs to be treated only once a week, so that patient compliance is better. In the future, increased intensity, more impulses, and a shortened interval would be tried to improve the curative effect.

ED has been linked to LUTS/BPH as a part of this syndrome. LUTS/BPH and ED share similar pathogenetic mechanisms such as chronic inflammation, vascular dysfunction, and hormonal alterations (Calogero, Burgio, Condorelli, Cannarella, & La Vignera, 2018, 2019). Exacerbations of LUTS are often accompanied by worsening of the IIEF-5 index. In this study, the application of perineal rESWT to the treatment of BPH caused improvement in LUTS accompanied by recovery of sexual function. Therefore, it can be speculated that the results of this study may be more effective than patients with ED who were not confirmed to have BPH and were treated for the penis with ESWT (De Oliveira, De Oliveira, Nunes, Martins, & Lopes, 2019; Kitrey et al., 2018). Besides, the perineal rESWT may improve the functional state of the bulbospongiosus and the ischiocavernosus, and the normal contraction of the two muscles assists in ejaculation. The ability of rESWT to enhance sexual function was discovered by chance during this research. In addition to the penis, the perineum would be increased as a treatment site for sexual dysfunction, because ED is closely related to the prostate disease.

Although the data look very promising, several limitations need to be strongly considered: (a) the follow-up period of only 3 months is short; hence, the durability of this approach is unknown, and the long-term data are awaited with interest, and (b) the number of cases is small with no control group, which represents a limitation. Despite the unknown mechanism of action and the limitations indicated above, this approach might indeed represent a significant advance. Basic research is also needed to clarify the therapeutic mechanism.

In conclusion, the noninvasive physical therapy with rESWT holds promise as a treatment for LUTS related to BPH. This procedure is potentially viable for a broad range of drug-refractory patients who are poor surgical candidates or not interested in surgery. This study may provide direction for the design and implementation of a multicenter, randomized, sham-controlled pivotal trial.

Declaration of Conflicting Interests

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