

INTERVENTIONS

Are Radial Pressure Waves Effective in Treating Erectile Dysfunction? A Systematic Review of Preclinical and Clinical Studies



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ABSTRACT

Introduction: Radial waves are used to treat erectile dysfunction; however, they are different than focal waves, and their mechanism of action or effect on improving this condition is not known.

Aim: To evaluate the effect of radial waves at the cellular level and their effectiveness at the clinical level for the treatment of erectile dysfunction.

Methods: Systematic literature review. Electronic database searches and manual searches were performed to identify (i) clinical trials or cohort studies evaluating the effectiveness of radial waves in men with erectile dysfunction and (ii) preclinical trials in animal models or cell cultures in which the production of nitric oxide or endothelial growth factor was evaluated. Study quality was assessed, and data were extracted from each study. A narrative synthesis of the results was performed given the high heterogeneity between the selected studies.

Main outcomes measures: Nitric oxide production, endothelial growth factor expression, and changes in the Erection Hardness Score (EHS) and the International Index of Erectile Function (IIEF) Questionnaire score.

Results: Four studies in animal models and 1 randomized clinical trial in men with erectile dysfunction and kidney transplantation were identified that met the selection criteria. Preclinical studies in animals suggest that radial waves increase cellular apoptosis in penile tissue, while vascular endothelial growth factor expression increases in brain tissue. In men with erectile dysfunction, no differences were found between radial wave therapy and placebo therapy in the mean IIEF score (15.6 ± 6.1 vs 16.6 ± 5.4 at 1 month after treatment), EHS (2.5 ± 0.85 vs 2.4 ± 0.7 at 1 month after treatment), or penile Doppler parameters.

Conclusions: No quality evidence was found to support the use of radial waves in humans for the treatment of erectile dysfunction. In animal models and at the cellular level, the results are contradictory. More research is needed. **Sandoval-Salinas C, Saffon JP, Corredor HA, et al. Are Radial Pressure Waves Effective in Treating Erectile Dysfunction? A Systematic Review of Preclinical and Clinical Studies. Sex Med 2021;9:100393.**

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Key Words: Erectile Dysfunction; Radial Wave Therapy; Low-Intensity Extracorporeal Shockwave Therapy; Systematic Review; Clinical Outcome; Clinical Trials

INTRODUCTION

Erectile dysfunction is a highly prevalent pathology in the entire male population, with a tendency to increase in the frequency of presentation as age increases.¹⁻³ The treatment of erectile dysfunction typically focuses on obtaining an erection through pharmacological or even surgical mechanisms. However, since 2010, shock waves have been evaluated as a new therapeutic option due to a large amount of evidence from cohort studies, controlled clinical trials, and meta-analysis⁴⁻⁹ suggesting that this type of wave generates benefits in some groups of patients with

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this disease and showing how the waves could act on the physiopathology of the dysfunction.¹⁰

Shock waves have been used in medicine since the late 1970s and early 1980s and are defined as sound waves produced when waves propagate “*through a medium at a speed faster than the speed of sound travels through that medium.*”¹¹ In focused and linear versions, shock waves have been evaluated for treating erectile dysfunction in clinical studies and animal models, showing beneficial results in erectile tissue, including increased levels of nitric oxide synthase (NOS) of endothelial and nervous origin, increased production of endothelial growth factor, the local recruitment of stem cells and Schwann cells, and the appearance of long-term neovascularization.¹²⁻¹⁴ Radial waves are low-pressure waves generated by the impact of two bodies, usually induced by pneumatic pressure, whereby they produce lower peak energy than shock waves. It is still not clear what radial waves mechanism of action is for the treatment of erectile dysfunction.

In the last decade and with the beginning of the management of erectile dysfunction with new technologies, these 2 types of waves have been used interchangeably in marketing campaigns and by some practitioners for penile shockwave treatment, assuming that they produce the same results.¹⁵

This systematic review aims to evaluate the effect of radial waves for the treatment of men with erectile dysfunction, as well as their effect on the production of compounds related to the erection or vascular function in animal models or cell cultures, answering two research questions: (i) In men with erectile dysfunction, what is the effect of radial wave therapy? And (ii) what is the effect of radial wave therapy at the cellular or tissue level?

MATERIAL AND METHODS

A systematic literature review was carried out in accordance with the guidelines proposed by the Cochrane Collaboration.¹⁶ The review started with two research questions (Table 1).

The study protocol was registered in the PROSPERO database (CRD42019123780) and did not require approval from the ethics committee.

Search Strategy

A search strategy was structured with MESH terms and free terms for each research question. Searches were performed in the electronic databases Medline, Embase, and Lilacs in January 2019. No language or date limits were used. Complementary searches were carried out in clinical trial registry databases (Cochrane Central Register of Controlled Trials-CENTRAL, clinicaltrials.gov, and International Clinical Trials Registry Platform-ICTRP), non-indexed sexual medicine journals, and Google Scholar. The search was updated in January 2021. The results of the searches in the different specialized databases were exported and organized in databases in Microsoft Excel version 2013.

Eligibility Criteria

For the first research question, randomized clinical trials, quasi-experimental studies, and cohort studies conducted in men diagnosed with vascular erectile dysfunction were included. For the second question, preclinical tests in cell culture or animal models were included for any disease that evaluated nitric oxide levels, the expression of endothelial growth factor (compounds related to the erection process), or other substances or outcomes related to vascular function or erection. Other inclusion criteria included manuscripts in press, gray literature, and papers available in English or Spanish with a report of any of the outcomes proposed in the PICOT question.

Publications not available as full text were excluded because these documents do not have enough information to assess the risk of bias; furthermore, the results may differ when the results are preliminary. When several publications of the same study were found, the most recent publication was included.

Studies Selection

Two researchers independently screened the manuscripts by title and abstract, verifying that they answered either of the two research questions and met the predefined eligibility criteria. Disagreements were resolved by a third researcher. Subsequently, the full text of the preselected studies was read to verify that they could be included in the review.

Table 1. PICOT structure for research questions

ITEM	Question 1. In men with erectile dysfunction, what is the effect of radial wave therapy?	Question 2. What is the effect of radial wave therapy at the cellular or tissue level?
Population	Men over 18 with erectile dysfunction.	Animals or cell culture
Intervention	Radial wave	
Comparisons	Sham therapy, focal shockwave therapy, or pharmacologic treatment	Sham therapy
Outcomes	Change in IIEF score Change in EHS score Change in Doppler Adverse events Quality of life	Nitric oxide levels Endothelial growth factor expression Substances or outcomes related to vascular function or erection Adverse events: cell damage, damage to sexual or reproductive function
Time	The one reported in the studies	Not applicable

Data Extraction

In a standardized format, the characteristics of the studies and the results reported in each article were extracted. The data extracted were: author, year, design study, population (n), interventions, outcomes reported (changes in the Erection Hardness Score (EHS) and the International Index of Erectile Function (IIEF) Questionnaire score, and adverse events in clinical trials; Nitric oxide production, endothelial growth factor expression, and others related to erectile function in preclinical studies), and device.

Quality Assessment

The risk of bias of the selected studies was independently assessed by 2 researchers, and disagreements were resolved by another researcher. For clinical trials, the Cochrane risk of bias tool was used,¹⁶ and for preclinical studies, SYRCLE's RoB tool was used;¹⁷ these 2 tools evaluate selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.

Data Synthesis and Analysis

A narrative synthesis of the results presented in each article was performed. Given that the selected studies presented highly

heterogeneous characteristics in their population and evaluated outcomes, the meta-analysis of the data was considered inappropriate.

RESULTS

Preclinical Evidence

Study Characteristics. A total of 398 studies were identified, of which four met the selection criteria and were included in the analysis of the results (Figure 1). The studies were published between 2008 and 2018;¹⁸⁻²¹ three studies were performed in male Sprague-Dawley rats (n = 70-105)¹⁸⁻²⁰ and one in male New Zealand white rabbits (n = 15-30)²¹. The studies evaluated different outcomes: level of vascular endothelial growth factor (VEGF),²⁰ proliferation, self-renewal of mesenchymal stem cells (MSCs),²¹ damage in neuromuscular transmission,¹⁹ apoptosis, and the hemodynamics of erection.¹⁸ Differences were also observed in the devices used (Swiss DolorClast or STORZ Medical) and the wave protocols applied (Table 2).

In the assessment of the risk of bias using SYRCLE's RoB tool, a high risk of selection bias was considered in all studies mainly due to nonconformities in the concealment and

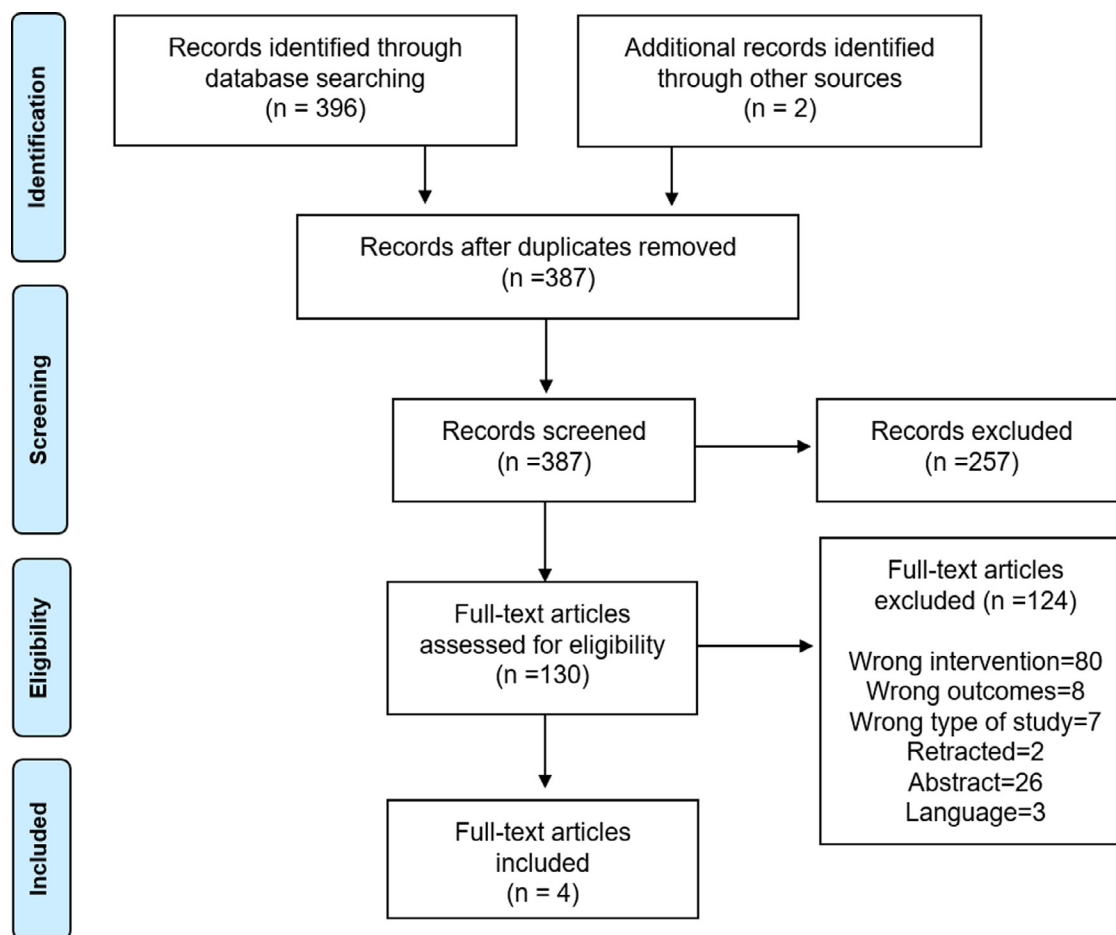


Figure 1. PRISMA flowchart preclinical studies.

Table 2. Characteristics of selected preclinical and clinical studies

Author / Year	Design study	Population (n)	Interventions	Outcomes related with ED	Device
Müller ¹⁸ / 2008	Animal testing in normal conditions	75 male Sprague-Dawley rats; 250–300 g	Group 1: high-dose/energy levels (HD), 2000 shock waves (sw) at 2 BAR, once a week for one session Group 2: high-dose/energy levels (HD), 2000 shock waves (sw) at 2 BAR, once a week for two sessions (9 HD groups) Group 3: high-dose/energy levels (HD), 2000 shock waves (sw) at 2 BAR, once a week for three sessions Group 2: low-dose/energy level groups (LD), 1000 sw at 1 BAR (3 LD groups).	1. Erectile hemodynamics evaluated with the intracavernous pressure/mean arterial pressure ratio (ICP/MAP). 2. Index for apoptotic cells.	Storz Medical Masterpuls MP100
Kenmoku ¹⁹ / 2012	Animal testing in normal conditions	70 male Sprague–Dawley rats; 8-week-old	2000 shock wave impulses at an energy flux density of 0.18 mJ/mm ² were applied to the right calf of each rat. The left calf of each rat was not treated and used as a control.	1. Muscle Injury and Complications 2. NMJ Morphometry	Swiss DolorClast, EMS, Nyon, Switzerland
Kang ²⁰ / 2017	Rat model of cerebral ischemia	105 Male Sprague Dawley (SD) rats (Liao Ning Chang Sheng Biotechnology, China, 240–260 g)	Group 1 (n=45): rESWT (1.0 bar, 200 impulses, 10 Hz directly on the right side of the head) 72 h after MCAO every 3 days. Group 2 (n=15): rESWT (1.0 bar, 200 impulses, 10 Hz directly on the right side of the head) 72 h after MCAO every 3 days. Also, the rats received rESWT (2.0 bar, 200 impulses, 10 Hz on the left side of the limbs) every 3 days beginning 6 days after MCAO. Control group (n=45). The rats in the control group did not receive it.	1. VEGF expression	STORZ Medical AG, Switzerland

(continued)

Table 2. Continued

Author / Year	Design study	Population (n)	Interventions	Outcomes related with ED	Device
Zhang ²¹ / 2018	Model in vitro and rabbit model	Human bone marrow-derived Mesenchymal Stem Cells (MSC) and 20 skeletally mature and healthy New Zealand White rabbits; male or female; 3–4 months old; 2–2.5 kg body weight	Shockwave-MSC preparation in a floating model: Radial shockwave treatment was conducted with continuous pulse, 1000 impulses, and 5 Hz (total treatment time, 200 s). Four groups were treated at different pressures: - Control: 0 bar - Experimental groups: 1 bar, 2 bars, and 3 bars. The healing effects of radial-shockwave-treated MSCs in vivo: To assess the healing effects of radial-shockwave-treated MSCs in vivo, cells were combined with polylacticcoglycolic acid (PLGA) scaffolds and implanted into the cartilage defects of a rabbit model.	1. MSC proliferation 2. MSC self-renewal	Swiss DolorClast Master (Electro Medical Systems SA, Switzerland).
Yamaçake ²² / 20189	Double-blinded, randomized, shamcontrolled trial.	20 men (10 patients in each group), age between 40 and 70 years, history of kidney transplant at least 6 months prior to the study, and diagnosis of ED for at least 6 months.	Intervention group: shockwaves were applied throughout the penile shaft (except the glans) and crura bilaterally by continuous movement of the applicator. 2000 shocks per session were applied with an energy intensity of 0.09 mJ/ mm ² . Control group: The sham treatment was performed using the same device. The probe was replaced by a similar device that emitted zero energy during treatment. It generated a noise and a feeling of popping at the treatment site.	1. Mean EHS score: After 1 and 4 months 2. Mean IIEF score: After 1, 4 and 12 months 3. IIEF score improvement 4. Penile Doppler parameters	Swiss Dolorclast® Smart with the EVO-BLUE transducer (Electro Medical Systems, Switzerland).

generation of the allocation sequence. Likewise, a high risk of performance and detection biases in all studies was considered. In contrast, the risk of attrition and publication biases was considered low, while the risk of other biases was unclear in two studies and low in the other two (Table 3).

Outcomes. Muller et al applied doses of 2000 (high dose) and 1000 (low dose) shock waves at 2 BAR to the penis of rats and evaluated the results on days 1, 7, and 28 to define the impact of radial waves at varying energy and/or dose levels at different time points on the functional and structural changes in erectile tissue. The results showed that in the groups that received low wave doses, hemodynamic parameters in erectile tissue, evaluated with the intracavernous pressure and/or mean arterial pressure ratio (ICP/MAP) was lower than in the control groups ($P < .05$); however, no significant differences were observed in the evaluation of smooth muscle-collagen relationships ($P > .05$).

Regarding the apoptotic index (AI), by which potential damage in the erectile tissue was quantified, it was significantly lower in all the low-dose groups compared to the high-dose groups, but the AI increased significantly compared to the control groups ($P < .01$). The authors of this study concluded that at both energy and/or dose levels, radial waves showed a time- and treatment-dependent reduction of the ICP/MAP ratio that could be mediated by apoptosis and collagenization of body smooth muscle.¹⁸

Kenmoku et al evaluated the changes in neuromuscular transmission after the application of shock waves to the right calf of 70 rats (control group: left calf) and found degenerated acetylcholine receptors in all treated muscles. In addition, the amplitude of the action potential on the treated side was significantly lower than on the control side after six weeks (27.9 vs 34.5, $P = .037$). On the other hand, no significant differences were observed in the transmission latency between groups, and it was found that the application of radial waves to the muscle induced a transient dysfunction of nerve conduction in the neuromuscular junctions.¹⁹

Kang et al evaluated the effect and underlying mechanisms of radial wave therapy in rats with cerebral ischemia (group 1 $n = 45$, group 2 $n = 15$, control group $n = 45$). Their results regarding VEGF expression levels showed a significant increase in the intervention group compared with the control group on days 12 and 30 ($2,017 \pm 0.05$ vs $1,661 \pm 0.05$; $P = .0097$ and 0.56 ± 0.08 vs 0.27 ± 0.06 ; $P = .027$, respectively).²⁰

Zhang et al investigated the effect of radial shock waves on human bone marrow mesenchymal stem cells (MSCs) using an in vitro model and subsequently evaluated the effectiveness of these cells on cartilage defects in vivo using a rabbit model. The results of the cell counts showed that treatment with radial shock waves at 2 bar significantly promoted the proliferation of MSCs and led to an increase of the number of cells in the S phase and a decrease in the number of cells arrested in the G0/G1 phase; slight increases in apoptosis rates and self-replicating activity of

MSCs were also observed. Additionally, radial shock waves favored osteogenic differentiation of MSCs but inhibited adipogenic activity.²¹

Clinical Evidence

Study Characteristics. The title and abstract of 237 studies were screened by two evaluators independently. In the full-text review, one study met the selection criteria (Figure 2). This study was a randomized clinical trial carried out in Brazil by Yamaçake et al²² in 20 men with kidney transplantation and erectile dysfunction. The intervention group ($n=10$) received 2 weekly radial wave therapy sessions every 3 weeks; in each session, 2000 shocks with an intensity of 0.09 mJ/mm^2 were applied, while the control group received sham therapy (Table 2). In the quality assessment, the risk of bias was considered unclear due to the differences between groups at the start of therapy.









































Outcomes. The mean IIEF scores after 1 and 3 months after finishing treatment were 15.6 ± 6.1 and 17.2 ± 5.7 in the wave group, respectively, and 16.6 ± 5.4 and 16.5 ± 5 in the control group. 70% of patients in the intervention group increased their baseline IIEF score by more than 5 points compared to 10% of the control group. The average EHS at the one month and 3-month follow-ups were 2.5 ± 0.85 and 2.4 ± 0.7 for the intervention group and 2.4 ± 0.7 and 2.6 ± 0.84 for the control group, respectively. Likewise, the penile Doppler parameters were similar between groups and did not show improvements compared to the initial evaluation.²²

DISCUSSION

After an extensive literature search, we found no head-to-head studies comparing the effect of radial waves versus focal waves on erectile function. Except for the study by Muller et al,¹⁸ in which apoptosis was evaluated to quantify the damage in erectile tissue after radial waves, and the ICP and/or MAP ratio during cavernous nerve stimulation was evaluated to assess erectile tissue hemodynamics, no other studies were identified that evaluated parameters of relevance to improve erectile dysfunction in specific penile tissue. However, we consider that the study by Kang et al,²⁰ carried out in brain tissue of mice, provides information of interest on the expression of endothelial growth factor and subsequent neovascularization and angiogenesis, which should be verified in erectile tissue. Likewise, the evaluation by Zhang et al²¹ of the effect of radial waves on MSCs proliferation and repopulation, is relevant for erectile function research, given the recent use of this therapy for erectile tissue recovery.^{23,24}

The study performed in men with erectile dysfunction identified in this review shows an effect that favors radial waves concerning the increase in the IIEF score compared to a control group but presents some considerations that limit the validity

Table 3. Assessment of risk of bias of studies in animal models

Type of bias	Domain	Item	Müller ¹⁸ 2008	Kenmoku ¹⁹ 2012	Kang ²⁰ 2017	Zang ²¹ 2018
Selection bias	Sequence generation	Describe the methods used, if any, to generate the allocation sequence in sufficient detail to allow an assessment whether it should produce comparable groups.	Unclear 	No 	No 	Unclear 
Selection bias	Baseline characteristics	Describe all the possible prognostic factors or animal characteristics, if any, that are compared in order to judge whether or not intervention and control groups were similar at the start of the experiment.	Unclear 	Yes 	Yes 	Yes 
Selection bias	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment.	No 	No 	No 	No 
Performance bias	Random housing	Describe all measures used, if any, to house the animals randomly within the animal room.	No 	No 	No 	Yes 
Performance bias	Blinding	Describe all measures used, if any, to blind trial caregivers and researchers from knowing which intervention each animal received. Provide any information relating to whether the intended blinding was effective.	No 	No 	No 	No 
Detection bias	Random outcome assessment	Describe whether or not animals were selected at random for outcome assessment, and which methods to select the animals, if any, were used.	Unclear 	No 	No 	No 
Detection bias	Blinding	Describe all measures used, if any, to blind outcome assessors from knowing which intervention each animal received. Provide any information relating to whether the intended blinding was effective.	No 	No 	No 	No 
Attrition bias	Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized animals), reasons for attrition or exclusions, and any re-inclusions in analyses for the review.	Yes 	Yes 	Yes 	Yes 
Reporting bias	Selective outcome reporting	State how selective outcome reporting was examined and what was found.	Yes 	Yes 	Yes 	Yes 
Other	Other sources of bias	State any important concerns about bias not covered by other domains in the tool.	Yes 	Unclear 	Unclear 	Yes 

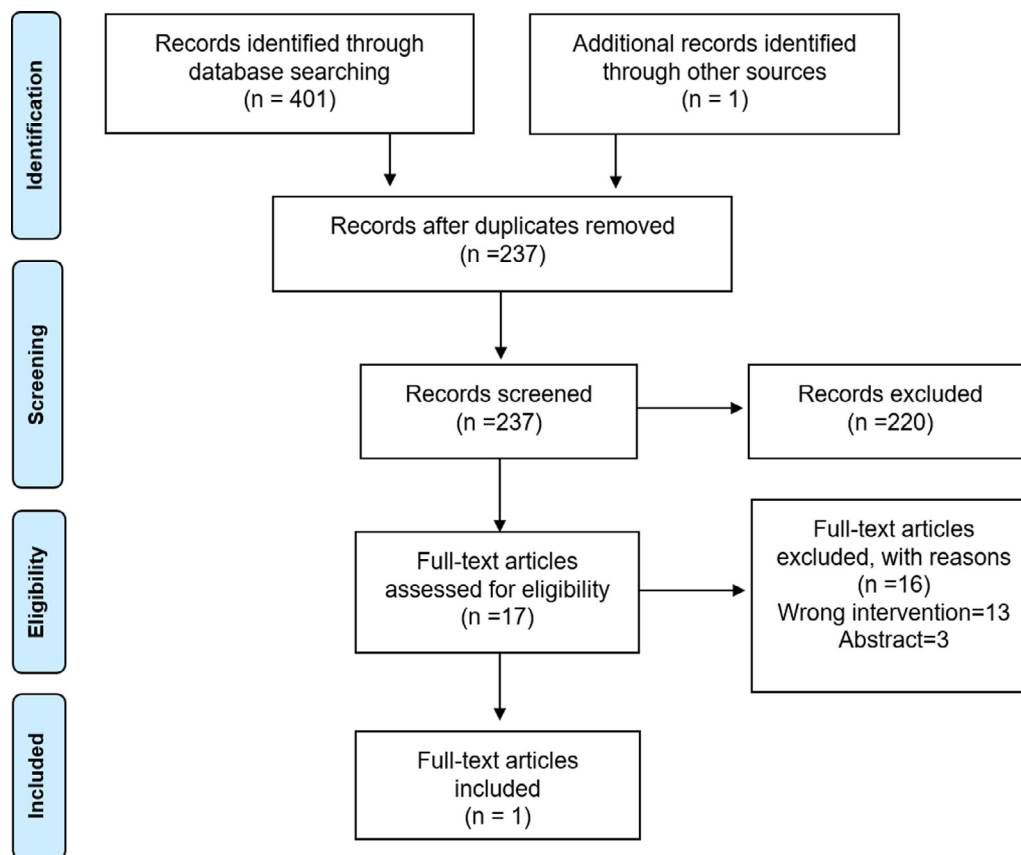


Figure 2. PRISMA flowchart clinical studies.

and applicability of their results, including the small sample size (10 patients per group), very specific population (men with kidney disease), baseline differences between the comparison groups, and the use of focal wave protocols for the application of radial waves²² that vary substantially in parameters, such as pressure, duration time and diffusion.¹¹

Radial wave devices for the treatment of erectile dysfunction are currently marketed as if they were focal waves, implying that they produce the same effect; however, the physical bases of radial and focal waves differ in the forms of expansion, amplitudes, and velocities of the waves.¹¹ Radial waves, also called ballistic waves, are a type of acoustic wave generated by the displacement of a projectile in a closed space propelled by high pressure-controlled air that leads to its acceleration in a probe, with its subsequent impact on an initial surface that transmits the force generated to the adjacent surface, forming waves of radial pressure and concentrating the maximum energy at the point of contact with the tissue, which is generally the skin; the waves dissipate as distance increases.²⁵

The difference between focal shock waves and radial waves is in the maximum pressure, which in the case of radial waves is 0.1 to 1 MPa; however, in focal waves, the maximum pressure can reach up to 100 MPa. Similarly, the pulse duration is 1 to 5 ms in radial waves and does not exceed 2 ms in focal waves.²⁵ Radial waves are often misnamed shock waves; however, they are

sound waves that reach a significantly lower maximum pressure than focal waves, have a slower rise time that does not exceed the speed of sound (essential for achieving the shock effect), and have radial or outward propagation without a focal point; that is, they do not have a shock effect and are not focal.^{11,26} Likewise, it remains to be proven whether radial waves produce cavitation effects like those produced by focal shock waves, an essential aspect for the biological effects of shock waves.^{11,26}

Moreover, from a regulatory viewpoint, radial wave devices are designated as class 1 medical devices, and this rating is given to devices that do not require regulatory approval in most countries or where they require minimal regulatory approval and can be used by minimally trained personnel, and no professional training is needed to administer them.¹¹ Conversely, focal shock wave devices, regardless of how they are generated (electrohydraulic, electromagnetic, and piezoelectric), are considered class 2 medical devices, require special premarketing permits, and must be used by specifically trained personnel because they can cause damage if they are used incorrectly.¹¹

This systematic review compiles information from preclinical and clinical studies to provide a view of the status of radial waves for the treatment of erectile dysfunction using systematic methods and standardized quality ratings. The principal limitation is the possible selection bias due to including only papers in English or Spanish, for which it is suggested that future studies

include other languages. Another limitation was the high heterogeneity between the studies, which did not allow statistical analysis. Additionally, the results of this review should be viewed with caution as there is a risk of bias in the included studies.

Finally, it is important to remember that the European Society for Sexual Medicine (ESSM) and Asia-Pacific Society for Sexual Medicine (APSSM) consider results on the efficacy of LISWT are controversial, due to the high heterogeneity of studies, the small number of patients included in clinical trials, and small estimates reported in pooled-data analysis, whereby its use is not yet recommended by these scientific societies.^{27,28}

CONCLUSIONS

Considering the differences between focal shock waves and ballistic or radial pressure waves, the latter should be considered a different technology that requires its own evidence before allowing its application in erectile dysfunction treatments. The preclinical and clinical evidence identified in this review is not conclusive and, in some cases, is contradictory, which is why studies with a more robust methodology are necessary to evaluate the effect of this type of wave on erectile function so that its use can be considered for the treatment of erectile dysfunction.

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STATEMENT OF AUTHORSHIP

Carolina Sandoval-Salinas: Conceptualization, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing, Supervision; José P. Saffon: Conceptualization, Methodology, Investigation, Writing – Original Draft, Funding Acquisition, Supervision; Hector A. Corredor: Investigation, Writing – Original Draft; Liliana Fonseca: Investigation; Laura Manrique: Investigation; Giovanni Solis: Investigation.

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SUPPLEMENTARY MATERIALS

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