STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

TITTLE OF THE STUDY:

RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF RADIAL WAVES FOR THE TREATMENT OF ERECTILE DYSFUNCTION

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RESEARCHERS:

JOSÉ PABLO SAFFÓN
CAROLINA SANDOVAL
JUAN MANUEL MARTINEZ
HÉCTOR CORREDOR
ANDRÉS FELIPE GALLEGO
OLGA URIBE

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Abstract

Background: Radial waves are an effective therapy for the management of various problems at the muscular and joint level, thanks to the effect it has on the activation of microcirculation. The effect of these waves on patients with erectile dysfunction is currently unknown; however, it is considered possible to help recovery in patients with vascular origin dysfunction by increasing microcirculation blood flow in this area.

Objective: To evaluate the efficacy and safety of radial shock waves for the treatment of erectile dysfunction.

Patients and methods: Randomized, double-blind clinical trial. The study will include patients of legal age with diagnosis of ED and score on the IIEF-EF scale between 11 and 21 points, who voluntarily decide to participate and sign the informed consent. Patients with bladder cancer, prostate cancer or active colon, ED of psychological origin, any psychiatric disorder, spinal cord injury, clinical suspicion of hypogonadism (AMS greater than 36), infections or active lesions of the penis or pubic area, ED secondary to treatment with medications (antiandrogenic therapy, use of corticosteroids, anti-Parkinson's, antipsychotics), radical prostatectomy or other radical pelvic surgery, history of pelvic radiotherapy, penile implantation, or endocrine diseases that occur with ED (acromegaly, gigantism, Addison's disease, hyperprolactinemia, androgenic deficiency), sickle cell anemia, and anticoagulated patients will be excluded.

Patients will be randomly assigned to one of the following treatment arms:

- **Arm 1 (Standard treatment (oral sildenafil) + Radial wave therapy)**: Sildenafil according to the degree of patient involvement + 6 sessions of radial waves. A weekly session of radial waves will be applied with the following parameters: 6000 pulses at 1.5-2.6 bar (depending on patient tolerance), with a frequency of 17Hz, the frequency should increase to 22HZ the first 500 impulses to create mild anesthesia in the area; in all radial wave sessions, 4000 impulses will be distributed in the body of the penis in scanning technique and 2000 impulses in the perineal area.

- **Arm 2 (Standard treatment (oral sildenafil) + Placebo therapy)**: Sildenafil according to the patient's degree of affectation + 6 sessions of placebo therapy. There will be a weekly session of placebo wave therapy, using the respective device to prevent the patient from receiving the radial wave. The same parameters of the "real" therapy will be used: 6000 pulses at 2.6 bar, with a frequency of 17 Hz; in all radial wave sessions, 4000 impulses will be distributed in the body of the penis in scanning technique and 2000 impulses in the perineal area.

Measurements will be made of the EHS and IIEF-EF scale scores, of the use of medication and of the possible adverse events of the therapy, at the beginning and end of the treatment, and one month after the therapies are finished.

Expected impact: Knowing the effectiveness and safety of radial waves for the treatment of erectile dysfunction will allow having a scientific basis for new treatment alternatives for men with this disease.

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to reach and / or maintain an erection sufficient to allow a satisfactory sexual relationship (1). Epidemiological information on ED shows that it is a condition that has a high prevalence and incidence worldwide and that mainly affects men over 40 years of age (2). The prevalence of ED in the general population of men under 40 years of age is approximately between 1% and 10% (3). Both prevalence and severity increase with age, in men between 60 and 69 years of age, the prevalence of erectile dysfunction increases from 20% to 40%, and this range can increase from 50% to 100% in men between 70 and 80 years old (3-6).

Currently, there are different pharmacological and non-pharmacological treatments for erectile dysfunction, among which are the administration of medicines for oral use, intracavernous and intraurethral, lifestyle modification, vacuum devices, psychotherapy, extracorporeal therapy with low intensity shock waves (Li-ESWT), vascular surgery for selected cases, and alternative therapies (7-14).

In addition to these treatments, the therapy with radial waves seems to be effective for the management of this pathology, since it increases microcirculation blood flow (15). Studies without a control group suggest improvement in the IIEF-5 scale of erectile dysfunction in patients who received this type of wave therapy, however there are no controlled studies to evaluate the effectiveness and safety of this therapy (16, 17)[1].

Boston Medical Group (BMG) is a global alliance of medical centers that share research information and treatment methods for male sexual dysfunction. This alliance has locations around the world that include Latin America, Europe, and the United States. In Colombia, Boston Medical Group aims to perform primary research in erectile dysfunction with the purpose of determining scientific evidence that allows the dissemination of research results that lead to a better understanding of ED, its diagnosis, treatment and prognosis. This will impact on the clinical management and finally on the health outcomes of patients with this condition.

The objective of this study is to determine the efficacy and safety of radial wave therapy for the treatment of patients with moderate to mild to moderate erectile dysfunction seen at BMG branches in Colombia and Peru.

[1] Pokorny P, Turcan P, Prochazka M, Prochazkova J. (2015). Evaluation of radial extracorporeal shock wave therapy in the treatment of erectile dysfunction. Journal of Sexual Medicine. 12. 233-233. /
Perelman J, Hepnar VD (2017) Men's Power-Pressure Wave Erectile Regeneration-Therapy: an Early Assessment. Urol Nephrol Open Access J 4 (4): 00136. DOI: 10.15406 / oneaj.2017.04.00136

Theoretical framework

Erectile dysfunction is the persistent inability to achieve and maintain an erection sufficient to allow a satisfactory sexual relationship (1). It is a benign problem related to the organic and psychological aspects of health that has a significant impact on the quality of life of the affected people and their families.

Research conducted in the United States reported a prevalence of ED between 44% and 52% in men between 40 and 70 years of age, 17.2% of which had minimal ED, 25.2% had moderate ED and 9.6% had complete ED (5). In Latin America the study "Erectile Dysfunction in North South America" (DENSA) reported that more than half of the respondents had some degree of ED (53.4%) with a higher prevalence of the minimum over the moderate or severe, the minimum ED had its peak in the population between 60 and 69 years, while moderate and severe was seen more in subjects between 70 and 79 years (18).

Among the risk factors associated with erectile dysfunction are cardiovascular disease, obesity, smoking, hypercholesterolemia, metabolic syndrome, major pelvic surgeries (radical prostatectomy of any kind), pelvic radiotherapy, prior priapism and trauma of cavernous or pelvic bodies (3,5,6). ED is a disease that occurs in many cases as comorbidity of other diseases in different proportions, for example, in 52% of hypertensive patients, in 64% of diabetics and in 90% of patients with depression (4, 11).

ED can be primary if it occurs from puberty and is usually associated with congenital vascular anomalies, or secondary, late onset after having a period of normal erectile function, associated with the aforementioned pathologies.

According to the etiology it can be predominantly psychogenic or predominantly organic, in which case it must be clarified whether its origin is vascular, endocrinological, neurological, induced by drugs, other causes or of mixed etiology.

There are several treatments for the management of erectile dysfunction. Among the most used are the so-called 5 phosphodiesterase inhibitors (PDE5 Inhibitors), however, they have not proven to have a healing effect on erectile dysfunction (19) and it is for this reason that options that can act on the physiological mechanisms that generate erectile dysfunction should be sought.

Radial wave therapy

Radial waves are pressure waves used for the treatment of different diseases of the musculoskeletal system. Among the differences with shock waves are the duration of the pulse, which is much longer.

Radial waves are generated by collision of solid bodies. The compressed air accelerates a projectile (bullet) that hits an impact body and part of the produced kinetic energy is transmitted to this body generating a translational movement in a short distance at a low speed until the coupled tissue or the hand piece decelerates its movement (15, 20).

The movement of the impact body is transferred to the patient's tissue at the point of contact, from where it propagates in the form of a radial pressure wave, which in the skin or superficial tissue is strong and decreases as it advances to deeper tissues (15, 20).

The effect of radial waves is less intense than focal shock waves, causes the disintegration of fibrosis and calcifications, and increases blood microcirculation and metabolic activity in the treated site (15, 20). There is evidence that radial wave therapy has a poor penetration to tissue (3cm), a low impact and limited biological effects (20, 21), however, this therapy has demonstrated effectiveness in the management of pain, muscle and tendon inflammation (15).

Although the effect of this type of waves is not known in erectile dysfunction, the effect on microcirculation increase suggests that it may be useful as a complementary therapy to the treatments currently used. In addition to this there is low-quality evidence that suggests a possible beneficial effect of radial waves.

Justification

Erectile dysfunction is a pathology with a moderate prevalence which increases and worsens as the population ages. It affects not only the sexual and reproductive health of the sufferer and his partner, but also his mental health, often producing disorders depressives that diminish the quality of life of people and their families.

Pharmacological treatment is not effective in 100% of patients and does not lead to changes in the physiology-pathology of erectile dysfunction (14), but acts as an adjuvant in the symptomatology, therefore, the management of erectile dysfunction should focus on the treatment of the pathophysiological causes that generate it and therefore other treatment options that can act in this way should be sought.

Therapy with (Li-ESWT) for erectile dysfunction has been proposed as a new alternative in the management of erectile dysfunction (12, 22-25). Its mechanisms of action can be multiple, but are summarized in the increase in vascular flow to the corpora cavernosa generated by a process of neovascularization (26) secondary to angiogenesis promoted by endothelial growth factors such as vascular endothelial growth factor (VEGF), endothelial cell growth factors and cell proliferation nuclear antigen (27), in addition to the increase in the concentration of vasodilator substances such as nitric oxide. The therapy with Li-ESWT has been presented as a therapeutic option, which does not replace the other alternatives, but which adds efficacy to traditional ED management (28).

Likewise, therapy with radial waves arises as a new option for the management of this disease, which has been conducted by different specialists given the benefit shown in the increase of blood flow and muscle recovery for different musculoskeletal conditions. However, currently there are no controlled studies that report on the efficacy and safety of this therapy for the treatment of erectile dysfunction (16, 17). For this reason, it is pertinent to carry out a clinical trial that allows obtaining valid results and thus making reliable clinical decisions.

Objectives

Primary

To evaluate the effectiveness of radial shock wave therapy in patients with moderate erectile dysfunction [2] measured as the increase in the average IIFE-EF score at the end of the treatment.

Secondary

1. To evaluate the effectiveness of radial shock wave therapy at one month of follow-up, with respect to the change in the average IIFE-EF score.
2. To evaluate the efficacy of radial shock wave therapy with respect to the average score of the erection hardness scale (EHS), at the end of the treatment and at one month of follow-up, in the intervention and control groups.
3. To evaluate the effectiveness of radial shockwave therapy, regarding the change in the use of sildenafil at the end of treatment and at one month of follow-up, in the intervention and control groups.
4. To compare the incidence of adverse events in the intervention and control groups.

[2] For this study moderate erectile dysfunction is considered a score on the IIEF-EF scale from 11 to 21, which includes the mild to moderate and moderate categories.

Materials and methods

Type of study

Randomized, double-blind clinical trial.

Research hypothesis

Ho: The change in the score of the IIEF-EF scale in patients with moderate erectile dysfunction[3], treated with radial wave therapy, is equal to those who receive placebo therapy.

Ha: The change in the score of the IIEF-EF scale increases at least five points in patients with moderate erectile dysfunction treated with radial wave therapy, compared with the score of patients receiving placebo therapy.

Study population

Patients diagnosed with erectile dysfunction of vascular origin who are treated at the Boston Medical Group facilities in Bogotá.

Inclusion criteria

1. Men older than 18 years
2. Erectile dysfunction presents for more than 3 months in more than 50% of intercourse.
3. IIEF-EF score between 11 and 21.
4. Patient who agrees to enter the study through the signing of an informed consent.

Exclusion criteria

1. EHS score of 4
2. Bladder, prostate or colon cancer.
3. Patients with ED of psychological origin.
4. Patients with spinal cord injury.
5. Patients with anticoagulant use.
6. Patients with sickle cell anemia.
7. Patients with clinical suspicion of hypogonadism (AMS greater than 36, Annex 1).
8. Patients with infections or active lesions of the penis or pubic area.
9. Patients with ED secondary to drug treatment (antiandrogenic therapy, antidepressants, use of corticosteroids, antiparkinsonians, antipsychotics).
10. Radical prostatectomy or other radical pelvic surgery.
11. Antecedents of pelvic radiotherapy.
12. Patients with penile implant.
13. Endocrine diseases that occur with ED: acromegaly, gigantism, Addison's disease, hyperprolactinemia, androgenic deficiency.
14. Patients with neurological diseases (Parkinson's, CVD, dementia of any origin)

[3] For this study moderate erectile dysfunction is considered a score on the IIEF-EF scale from 11 to 21, which includes the mild to moderate and moderate categories.

Sample size

Assuming that the placebo plus drug group has an average change in the score of the IFE-EF scale of 5 points and that the new wave therapy must have an additional change of at least 5 points to be considered clinically relevant, for a power of 80% and a one-tailed level of significance of 97.5%, with a standard deviation of 8 points, a sample size of 33 patients was estimated for each group. Adjusting for a percentage of losses of 20%, the size per group is 40 patients, for a total of 80 patients in the study. These calculations were performed in Stata 15.1®.

Interventions

Each patient will be assigned randomly to one of the following groups:

- **Arm 1 (Radial wave therapy + oral treatment)**: 6 radial waves' sessions. A weekly session of radial waves will be applied with the following parameters: 6000 pulses at 1.5-2.6 bar (depending on patient tolerance), with a frequency of 17Hz, the frequency should increase to 22HZ the first 500 impulses to create mild anesthesia in the area; in all the sessions of radial waves, 4000 impulses will be distributed in the body of the penis in scanning technique and 2000 impulses in the perineal area, specifically in the ischiocavernosus and bilateral bulbo-sponge muscles. During the period of therapy application, patients will receive oral treatment with sildenafil [4] according to the patient's degree of affectation.

- **Arm 2 (Placebo therapy + oral treatment)**: 6 sessions of placebo therapy. There will be a weekly session of placebo wave therapy, using the respective device to prevent the patient from receiving the radial wave. The same parameters of the "real" therapy will be used: 6000 pulses at 2.6 bar, with a frequency of 17 Hz; in all the sessions of radial waves, 4000 impulses will be distributed in the body of the penis in scanning technique and 2000 impulses in the perineal area. During the period of therapy application, patients will receive oral treatment with sildenafil [5] according to the patient's degree of affectation.

The radial waves will be administered with the Masterpuls MP50 device from Storz medical.

Primary Outcome

The primary outcome of this study is the difference in the average score of the IIEF-EF scale (Annex 3) in at least 5 points at the end of the treatment.

Secondary outcomes

- IIEF-EF score after one month of follow-up.
- Erection Hardness Score (EHS) at the end of treatment and one month follow-up: The EHS is a unique Likert scale and the version validated in Spanish (35) will be used, which has the following score, 0: The penis does not change in size or hardness; 1: The penis increases in size but does

[4] This is the standard treatment.

[5] This is the standard treatment

not become rigid; 2: The penis is rigid but not enough to penetrate; 3: The penis is rigid enough for penetration but not completely hard; and 4: The penis is completely hard or rigid (Annex 4).
- Change in the dose or use of sildenafil.
- Incidence of adverse events.

Safety

It will be determined by the presence of adverse events. These will be evaluated at the end of each of the therapies and a month of follow-up. This variable will be dichotomous as the presence or absence of adverse events. Additionally the type of adverse event and the degree of severity will be recorded.

Randomization

The assignment of patients to the treatment arms will be done with the method of randomization by balanced blocks of unequal cells. The assignment of the treatment will be centralized, so once the patient agrees to participate in the study and signs the informed consent, an email should be sent to the research center (csandoval@bostonmedical.com.co) who will only inform the therapist which is the group (intervention or control) that corresponds to the patient.

To conceal the assignment sealed opaque envelopes will be used, this envelope will be opened once the request is generated in each center, after the patient has voluntarily accepted to participate in the study and the informed consent process has been carried out with signature of the written document.

Neither the patient, the attending physician, nor the professional who applies the questionnaires will know the group to which the patient was assigned.

Techniques, procedures, data collection and processing

The subjects who attend consultation for erectile dysfunction at the Boston Medical Group clinics in Bogotá (Colombia) and Lima (Peru), will be treated as usual according to the institutional management protocols and screened to determine if they meet the eligibility criteria. If so, they will be invited to participate in the research project and the informed consent process will be carried out in which the objectives, risks, benefits, procedures and other relevant research data will be explained.

Once the patient has voluntarily accepted to participate in the study and the informed consent document has been signed, an email will be generated to the research center to request the group to which the patient will be assigned.

A baseline measurement of the IIEF-EF and the EHS will be made before starting the intervention; In addition, the AMS questionnaire should be completed to rule out hypogonadism. Once the treatment is completed, patients must complete the IIEF-EF and EHS scales in the last treatment session. In this same session, the patient will be evaluated for adverse events; later, they will have

a medical follow-up one month after the end of the treatment, in which measurements of effectiveness and safety of the therapy will be made again. If the patient cannot attend the medical follow-up, the surveys will be sent by email on the day of the follow-up appointment and the patient will be contacted by telephone (Figure 2).

Radial wave therapy will be applied with the following parameters: There will be a weekly session of 6 sessions of radial waves. A weekly session of radial waves will be applied with the following parameters: 6000 pulses at 1.5-2.6 bar (depending on patient tolerance), with a frequency of 17Hz, the frequency should increase to 22HZ the first 500 impulses to create mild anesthesia in the area; in all the sessions of radial waves, 4000 impulses will be distributed in the body of the penis in scanning technique and 2000 impulses in the perineal area. The application at the perineal level should be performed with the patient in the supine position in a low lithotomy position, the testicles should be slightly raised to apply the wave on the perineal musculature (ischiocavernosus and bilateral bulbospongiosus).

The placebo therapy will be done with the same machine and the same parameters as the actual therapy, but the adjustment will be made in the handpiece to eliminate the effect of the radial waves.

If there is a difference between placebo therapy and radial wave therapy, patients in the placebo arm will receive the intervention arm scheme, one month after the initial treatment.

All clinical data will be recorded in the electronic medical record of Boston Medical Group and in the database of the study, in the latter a code will be used for the identification of research subjects, thus avoiding the use of the personal patient data. At the end of the collection of the total sample, the missing clinical information will be extracted from the electronic medical record. This information will be exported to a flat file for the corresponding statistical analysis.

The research team will hold meetings every two weeks to monitor the study to validate the data of the base.

Follow-up

The research subjects will be followed up one month after the end of the treatment. In the event that the patient cannot attend the follow-up, the respective scales will be sent to his e-mail so he can process them and return them by the same means; if after 3 days no response is received, a research assistant will call him and apply the questionnaires by telephone.

Statistical Analysis

A descriptive analysis of the individuals' baseline characteristics linked to each treatment arm will be made, estimating measures of central tendency and dispersion in the case of continuous variables, and measures of relative and absolute frequency for categorical variables.

To evaluate the effectiveness of the therapy, the change in the IIEF-EF scale will be compared at the end of the treatment with the baseline score for each of the arms, using parametric tests in case the

data present a normal distribution, or nonparametric tests otherwise. This same analysis will be done for the scores at the one-month follow-up.

For the EHS scale, the change in at least 1 point will be evaluated, in any of the established measurements. The association between the change in the score and the received treatment will be evaluated estimating the relative risk with its respective confidence interval.

The percentage of patients that decrease or discontinue the use of sildenafil in each group will be estimated, comparing the proportion between the groups at the end of the therapy scheme and the month of follow-up, using the Chi-square test.

The incidence of adverse events for each of the intervention groups will be estimated and the value between them will be compared using the Chi-square test.

In addition to the comparison between groups, stratified analyzes will be performed with multivariate regression models to determine how each intervention adjusted for covariates, such as comorbidities or additional treatments.

An interim analysis will be done once 60% of the total number of patients has completed the treatment (main outcome).

Expected impact

The main contribution of this study is for the scientific community and for patients with erectile dysfunction, by collecting scientific evidence of quality that allows to make a decision about the use of radial waves for the management of erectile dysfunction.

Ethical aspects

The research will be conducted in compliance with the legal and ethical guidelines described in Resolution 8430 of 1993 of the Colombian Ministry of Health and other national regulations; The principles for human research enunciated in the Declaration of Helsinki of the World Medical Association, and the ethical guidelines contemplated by the Council of International Organizations of Medical Sciences -CIOMS and the Belmont Report- will be respected and complied with.

According to Article 11 of Resolution 8430 of 1993 of the Ministry of Health, it is considered that this is an investigation with risk greater than the minimum for the research subjects, which fully respects the provisions of article 8 of the same. On the other hand, and in accordance with this legislation, approval will be requested from an Ethics Committee that authorizes the development of the investigation.

The intervention to be evaluated has a proven effectiveness in other conditions and the reports published in scientific evidence show that the rate of adverse events is very low. The intervention will be administered by personnel with all the technical capacity and experience required, both for the administration of the intervention and for the management of possible adverse events.

Each subject will be informed of all possible consequences (regardless of their probability of occurrence) of participating in this investigation. An informed consent will be explained and completed and the individual will be free to accept participation in the study without causing any inconvenience with their treatment (Annex 5).

Likewise, the confidential management of the information collected in response to the need not to violate the privacy of each research subject will be guaranteed. The databases will be kept in the Boston Medical Group offices and will only be accessed by the researchers participating in the study.

It is guaranteed that the researchers possess the technical competence required for this study and that they have the necessary tools for the care and use of research data.