Radiofrequency energy in the treatment of erectile dysfunction – a novel cohort pilot study on safety, applicability, and short-term efficacy

Ilan Gruenwald (i_gruenwald@rambam.health.gov.il)
rambam https://orcid.org/0000-0003-0330-2859
Boaz Appel
Arik Shechter
Rambam Healthcare Campus https://orcid.org/0000-0001-8270-8069
Alexander Greestein

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Abstract

Collagen is an essential component of the structures involved in the erectile mechanism and as such, impaired collagen may hinder it. Because Radiofrequency (RF) energy has been shown to renew and restore spatial structural arrangement of collagen fibers, treatment of ED with RF could lead to anatomical and physiological changes at the penile tissue level and could lead to improvement in the erectile mechanism. We conducted this study to assess the effect of RF treatment on erection quality. We evaluated the safety, applicability, and efficacy of a self-applied, handheld, low-intensity radiofrequency device (Vertica®) in men with moderate and mild-to-moderate organic ED. The treatment protocol consisted of 12 treatments (twice a week during the 1st month, and once a week during the 2nd month), each participant treated himself individually. Treatment outcomes were evaluated using the International Index of Erectile Function (IIEF-15), Erection Hardness Scale (EHS), Erectile Dysfunction Index of Treatment Satisfaction (EDITS), Benefit, Satisfaction & Willingness to continue (BSW), Quality of Erection Questionnaire (QEQ), Sexual Quality of Life (SQOL) questionnaires and specific questions addressing side-effects and ease of use. Twenty-eight out of 32 men (mean age 59.5.7 ± 9.8, range: 41-78y) completed a one-month follow-up after treatment. Mean IIEF-15 (43.7. ±7.8 vs 60.9 ± 10.8, $p < 0.01$), IIEF-Erection Function domain (IIEF-EF) (16.8 ± 3.1 vs. 24.4 ± 4.4, $p < 0.001$), and EHS scores (2.2 ± 0.8 vs. 3.2 ± 0.5, $p = 0.01$) were all significantly improved. Fifty percent of patients achieved normal EF parameters (IIEF-EF score ≥ 25). High mean scores were achieved in the EDITS (76.8 ± 20.3), BSW (4.83 ± 1.1), QEQ (73.4 ± 23.8), and SQOL (67 ± 29.4) questionnaires. No side effects were reported and participants rated the device as very comfortable, simple, and easy to operate.

Introduction

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to attain and/or maintain a penile erection sufficient for sexual satisfaction[1]. The worldwide prevalence of ED is estimated to be up to about 80% in adults, and increases with age [2].

The quest for an ED treatment modality that would provide a rehabilitative or curative impact for ED and would put an end to coupling the treatment to sexual activity is still ongoing. Most contemporary treatments (e.g., oral medications, intracorporal injections, or use of a vacuum-constriction device) require timing treatment before any expected sexual activity, negatively affecting the spontaneity of any sexual activity and leading to a less satisfying relationship [3].

In the recent years, applying external energy to the penis emerged as a new concept of treatment to improve erection quality. Such treatment is not applied prior to sexual activity, and therefore eliminates the need to time and schedule ahead the use of medications before sexual activity and intercourse, consequently restoring spontaneity to sex life. Low-Intensity Shockwave Therapy (LI-ESWT) which results in micro-anatomical and physiological changes at the level of the cavernosal tissue is one form of such treatment modality [4]. Radiofrequency (RF) energy has been shown to renew collagen and to restore their spatial structural arrangement in various tissue fibers due to its heating effect [5]. Collagen layers are

present abundantly in the tunica albuginea (TA), and in the corpora cavernosa. We hypothesise that applying RF to penile tissues may trigger remodeling of the collagen in those tissues that are involved in the erectile mechanism. In addition, hyperthermia may promote upregulation of nitric oxide synthase involved in the erectile mechanism.[6] These mechanisms triggered by RF may act synergistically to improve the quality of erection. We conducted our study to evaluate the safety, applicability, and efficacy of a self-applied RF handheld device for the treatment of ED.

Methods

Study population:

Men 40–85 years old with mild or mild-to-moderate organic ED (IIEF-EF scores between11-20) with an ED duration of 6 months and a stable relationship for at least three months comprised the study population. The diagnosis of organic ED was based on a medical and sexual history. The study protocol was reviewed and approved by the local institutional review board and each participant gave his written informed consent to participate in this study.

Patients using phosphodiesterase type 5 inhibitors (PDE5i) treatment were not excluded and were instructed to adhere to their routine pattern of treatment during the whole study period. Excluded were men with any penile dermatologic disease or lesion, micropenis, history of penile carcinoma, penile piercing, penile prosthesis, Peyronie's disease, documented urethral stricture, sensory disorders, and any known allergy to aqueous gel.

Device: The Vertica® (Ohhmed, Israel), is a computerized hand-held device that generates pulses of RF energy delivered at a frequency of 1Mhz. into the penis via 3 couples of electrodes, creating an internal thermal heating effect. (Photo 1). The temperature in the corpora cavernosa and the surrounding TA reaches 41–43ºC. The level of energy is fully controlled by the patient, increasing, or decreasing it via the + and - buttons on the control panel of the device (Photo 2) according to the heat sensation on the penis.

The Vertica® (Ohhmed, Tiberius, Israel) consists of two parts. One is a handheld ring into which the penis is placed. The ring component contains a circle of electrodes that deliver the RF energy in a predetermined digitally revolving order to the corpora cavernosa, encompassing the penis without covering the urethra or the neurovascular bundle area, as the electrodes in the these areas (12 and six o'clock) are inactive and do not deliver RF energy, The second part is a pad that contains 3 electrodes that are used for RF energy delivery and is placed at the perineal area, covering the crural region of the penis while sparing the urethral area (Photo 3).

As a safety measure, all the electrodes have a built-in thermistor that is set to immediately stop the energy discharge whenever the skin temperature level on the skin reaches 40ºC. As an additional safety measure in order to deliver the RF energy, the patient is required to press the "treatment" button continuously for operating the device, thus in any situation in which the patient feels any discomfort, he

can immediately shut the energy delivery off by simply removing the finger from the "treatment" button (Photo 2).

Protocol:

The study was conducted between 2018–2019. Patients attending the neuro-urology unit complaining of ED were recruited. None of them received incentives of any form. The device was supplied by the manufacturer (Ohhmed, Tiberius, Israel). All men received a short explanation on the operation of the device. After applying an aqua gel on the penile shaft, the penis is placed into the electrode ring of the handheld piece and the perineal electrode pad is placed at the perineal area. During the treatment session, to cover the whole penile pendulous part, the patient slowly slides the Vertica® from the base of the penis, along the shaft to the distal part (the corona sulcus line), applying the preferred intensity of RF by self-controlling the heat level at the penis. Each treatment session starts with the lowest intensity level and the patient then gradually increases it until he reaches his individually comfortable heat intensity. Each participant treated himself individually with the Vertica® device at the Neuro-Urology unit, Rambam Medical Center, initially under the guidance of the investigator until complete adequate operation by the patient was achieved. This took no more than 2 sessions. Treatment protocol was based on the dermal treatment protocols. The patient was then left alone in a private room for continuing self-treatment. The treatment protocol consisted of 12 treatments (twice a week during the 1st month, and once a week during the 2nd month). Each treatment session duration at the clinic was 30 minutes,15 minutes with the ring part, and additional 15 minutes with both the ring and pad.

Baseline status and outcomes were evaluated before treatment and one month after completion of all 12 treatment sessions, using IIEF-15, IIEF-EF, Erection Hardness Scale (EHS). For evaluation of their status post treatment, Erectile Dysfunction Index of Treatment Satisfaction (EDITS), Satisfaction Willingness to continue (BSW), Quality of Erection Questionnaire (QEQ) and Sexual Quality of Life (SQOL) questionnaires. All questionnaires used in the study were professionally translated to Hebrew. These questionnaires are accepted and used by the urological community clinical and research tools in Israel. As outcome measure of success we used the strict criteria for minimal clinical significant improvement of quality of erections, defined by the MCID (Minimal Clinical Important Difference) of the IIEF-EF [7]

Specific questions addressing safety and side-effects (pain, fever, burning, discomfort, urinary disorders) and ease of use were handed each session. The International Prostate Symptom Score (IPSS) was used to evaluate any possible deleterious effect on micturition. Patients on PDE5i treatment were constantly and actively followed up for confirming their use of PDE5i during the whole study duration, and all the evaluations at baseline and at follow-up reflected the patients' erectile function while using the medication.

In addition, the first 10 participants underwent a penile Flow Mediated Dilatation (FMD) study. This is a modified plethysmography measure at the penile level, done in the flaccid state. The technique includes a rapid cessation of a 3–5 minutes' ischemic period (achieved by using a designated strain gauge). This

technique aims to assess arterial elasticity representing penile endothelial function and was performed at baseline and 1 month after the last (12th) treatment [8] [9].

Statistical analysis:

For analysis of sample size for an 80% power with a 5% level of significance, we used a sample size calculator for comparing paired differences in IIEF-EF for mean score changes of 4.0 ± 4.0 resulting in a need for 10 participants. Calculating the sample size assessment for our 28 participants, a power of 95% was reached.

Descriptive statistics in terms of mean, standard deviation, median and percentage were calculated to all parameters in the study. Wilcoxon Signed Ranks Test was used to test the differences between IIEF − 15 for IIEF-EF at baseline vs. one-month after ending treatment.

Repeated measure model was demonstrated to test the changes of IIEF-EF at baseline vs. one-month after ending treatment when controlling for combined treatment, age < 60, age ≥ 60 and for ED duration at 3 categories: <12 months, 18–24 months and > 30 months.

SPSS version 28 was used for all statistical analysis. The statistical significance level was set as $p < 0.05$.

Results

Thirty-two men were recruited. Four of the 32 participants were withdrawn from results analysis due to protocol violation, not due to side effects related to the treatment: one due to separation from his steady partner, one due to COVID-19 restrictions, one due to evaluation of a new incidental pathologic finding in the lungs, and one due to unexpected personal issues necessitating traveling abroad.

Twenty-eight out of 32 men with ED (mean age 59.5 ± 9.8, range: 41-78y), completed the entire treatment protocol and one-month follow-up. Their average ED duration was 41.4 ± 30.6: range 6 to 120 months.

Overall, a statistically significant improvement was demonstrated in the IIEF-15 (43.7 ± 7.8 vs 60.9 ± 10.8, $p < 0.01$), IIEF-EF (16.8 ± 3.1 vs. 24.4 ± 4.4, $p < 0.01$). (Table 1). Fourteen out of twenty-eight (50%) reached normal EF parameters (IIEF-EF score ≥ 25). only 3 patients did not meet the MCID criteria and were considered failures.

EHS scores (2.2 ± 0.8 vs. 3.2 ± 0.5, $p < 0.001$) when comparing baseline parameters to one month after ending treatment. 25/28 improved their erections according to the IIEF-EF MCID criteria. (Table 1). At baseline, 13 (46.4%) reported an EHS of 3, 8 (28.5%) reported an EHS 2 and 7 (25%) reported EHS 1. Following treatment,19 (67.8%) reported an EHS of 3, 7 (25%) reported EHS score of 4 and 2 patients reported and EHS 2 (7.1%). None of the patients reported an EHS of 1, (Graph 1).

Sexual desire domain was the only domain of the IIEF-15 that did not improve significantly (7.59 ± 1.46 vs. 8.08 ± 1.29; $p = 0.23$) (Table 1).

Since 8/28 patients were using PDE5is, we compared IIEF-EF scores according to use (n = 8) and non-use (n = 20) of PDE5Is. Mean IIEF-EF scores increased significantly in both groups, (fom 17.45 ± 2.64 to 25.1 ± 4.54, p < 0.001), and from (16.29 ± 3.40 to 24.0 ± 4.47 p = 0.005)) respectively, without a statistically significant difference between the two groups (p = 0.13) (Graph 2).

When analyzing IIEF-EF scores of the participants according to age groups, the young (< 60) and old (≥ 60) age group. IIEF-EF scores improved significantly in both age groups (16.47 ± 2.99 to 24.4 ± 5.35; p < 0.001) and (18.0 ± 2.48 vs. 25.33 ± 3.17, p < 0.001.) respectively, Without a statistically significant difference between the two age groups (P = 0.69).

When analyzing IIEF-EF scores of the participants according to ED duration;<12 months, 13–24 months and > 25 months, a statistically significant improvement was demonstrated in all three ED duration groups (18.8 ± 2.38 vs 27.2 ± 3.83, p < 0.004, 17.8 ± 2.95 vs 26.4 ± 4.21, p = 0.015, and 15.9 ± 2.77 vs 23.42 ± 4.96, p < 0.001), respectively without a statistically significant difference between the three ED duration groups. (p = 0.84).

High scores were achieved in the EDITS (76.8 ± 20.3), BSW (4.83 ± 1.1), QEQ (73.4 ± 23.8) and SQOL (67 ± 29.4), questionnaires (Table 1).

Quantified endothelial function improved significantly in all 3 FMD parameters; baseline flow, max flow and area under the curve (blood volume) by 53%, 124% and 125%, respectively (Table 1).

No significant deleterious effect of the treatment on lower urinary tract symptoms was demonstrated by the IPSS questionnaire (9.40 ± 7.48 vs. 8.49 ± 6.8, p = 0.6).

Twelve participants reported re-appearance or improved morning erections, without being directly asked about it. No side effects such as pain, fever, burning sensation, local pressure, discomfort and dysuria were reported, nor any dropouts due to side effects occurred. Participants rated the device as very comfortable and easy to operate.

Discussion

In this proof-of-concept study, we were able to confirm that RF treatment for ED is effective, safe and easily applicable. We demonstrated statistically significant improvement in all IIEF-15 domains, except for the sexual desire domain. The improvement in erectile function was prominently emphasized by the EHS scores, as at baseline only 46.4% reported an EHS score of 3 (penis is hard enough for penetration but not completely hard) while following treatment 67.8% reported an EHS score 3 and an additional 25% an EHS score of 4 (Penis is completely hard and fully rigid) while none reported an EHS score of 1 (Graph. 1).

Our interest in applying RF as external physical energy to the penis for the treatment of ED evolved from the documented beneficial results of LI-ESWT applied to the penis for ED treatment [4][10]. RF, which is routinely used in medicine, is a type of electric current between two electrodes.[11] When applied at low

frequencies, it causes interactions between charged molecules and ions and creates heat within the tissue. The heat causes collagen fibers to undergo structural changes, resulting in the remolding of new collagen and elastin fibers[12] [13]. This type of low-intensity RF is currently used in the dermatology field to improve skin laxity and treat cellulite and wrinkles[14] These treatments are based on several laboratory research studies showing a statistically significant increase in collagen types I and III, consisting of newly synthesized collagen found in the histology of the human skin following RF treatment .[15]. Zelickson et al, using a bovine tendon histological and ultrastructural model of an RF application, documented dermal remodeling with new collagen regeneration[16]. In addition, rearrangements of collagen tissue were found in vaginal wall biopsies before and after RF application in postmenopausal women who were treated for stress urinary incontinence [17].

The rationale for improving erection quality by altering collagen characteristics is based on the fact that during erection, the increase in intracavernosal pressure depends, among others, on the integrity and function of the fibro-elastic components (collagen and elastin) within the sinusoids and within the TA[18].

Collagen types I and III are mainly present in the TA, interlaced with elastin fibers, and involved in the compression of the emissary veins. In addition, the corpora cavernosa contains an evident amount of collagen type IV[19]

Collagen IV is the major structural scaffold of the intracavernosal pillars which have an important role in maintaining the cylindrical shape, strength, and rigidity of the penis during erection, and they also significantly contribute to the regulation of the intracorporal pressure during erection [20][21] Collagen type IV also constitutes the scaffold of the basal membranes in the corpora cavernosa tissue, providing more flexibility and support to the vessels[22]. It is important to note that in recent years the basal membrane area has also been recognized as an important regulator of cell behavior, probably serving as an extracellular microenvironment sensor for endothelial cells[23]. At the penile level, the basal membrane may play a role in tissue and organ morphogenesis and angiogenesis. Collagen type IV is ideally suited for the incorporation of laminins, molecules that interact with receptors and regulate multiple cellular activities and signaling pathways [22]. Therefore, our assumption is that remodeling these components in both corpora and TA by application of low-intensity RF may improve and restore erectile quality.

Remodeling collagen by applying RF energy is a biological process that lasts approximately three months [23]. We documented favorable results as early as 4 weeks, which merit further discussion. However, similar early results were also reported following treatment of ED by other external energy sources such as LISWT[24]. According to Ciampa et al., the peak expression of the neovascularization response following LI-ESWT occurs as early as 4 weeks after treatment, which may be related to the nitric oxide (NO) mechanism.[25] Cavernosal NO activity may be enhanced by the direct effect of the higher temperature leading to vasodilation and increased blood flow, consequently leading to increases in penile PO2. High oxygen tension arterial levels promote the activation eNOs and nNOs (mediators involved in the erectile mechanism)[25, 26, 27].

Activation of these enzymes by increased temperature was demonstrated in several laboratory studies; Ilangovan et al. demonstrated that eNOs is induced in cultured endothelial cells when exposed to mild heat (42^{o}C), and concluded that induced heat may upregulate NO synthase in cardiac cells [6]. Harris et al, in a Bovine aortic endothelial cells model, reported that incubation of cells for 1 h at 42^{o}C was associated with increased eNOs activity, agonist-stimulated NO release, and a decreased vasoconstrictor response [27]. The penile hemodynamic changes in our study were verified objectively by penile FMD in all three measured parameters. Furthermore, our FMD results after RF treatment are in concert with data presented by Mamede et al using Duplex ultrasound and showing that RF energy improves hemodynamic parameters [28].

We expect to achieve a sustained effect of ED improvement similar to the reported dermal RF protocols [16], which is explained by vascular changes leading to physiological variations. The adventitial tissue that surrounds the penile arterioles responds to arterial "injury" by activating its resident progenitor cells and induces the process of collagenesis and angiogenesis [29–31]. The repeated heat caused by RF to the penis applied during the protocol we used, may induce the same “injury” effect and promote the remodeling of vascular cavernosal body components. In addition, Korshunov et al reported that the local heat dissipated by RF energy triggers endothelial cell interaction with medial and adventitial cells and may contribute to vascular remodeling[32]

Another possible mechanism for the early RF effects is the fact that heating by RF is volumetric, and a reverse thermal gradient is created, causing small amounts of transudate to accumulate in the extracellular matrix. A mild perivascular infiltrate after RF treatment has already been documented [33] [16]. This natural inflammatory process could by itself trigger angiogenesis and collagenesis, but we can assume that some of the fluid remains in the extracellular matrix. Following repeated exposures to RF treatment, accumulation of extracellular fluid contributes to better compression of the draining venules against the TA inner wall during the following events of increased intracorporal pressure, clinically expressed as improved erections.

We used questionnaires for outcome assessments because some data such as severity and frequency of sexual function is better assessed in real life settings using patient reported outcomes (PROs), avoiding elaborated laboratory-based diagnostic testing [34]. Therefore, evaluation was done primarily based on PROs, leaving out nocturnal penile tumescence test, omitting a PDE5i washout period and allowing the participants to continue their routine sexual activity pattern. IIEF-15 served only in the initial evaluation of the patients as an additional tool for exclusion/inclusion of the patients. Nevertheless, due to the innovative nature of our study, and to have a better understanding of the underlying hemodynamic changes induced by RF treatment, we decided to apply the FMD test in a cohort of ten participants before and one month after completion of all RF sessions.

To the best of our knowledge, this is the first study in the English literature in which a beneficial effect of RF on ED was proven by using the contemporary ED evaluation protocols. However, our study served merely as a proof-of-concept trial. The small number of patients, lack of a sham-controlled group and

short-term follow-up are its main limitations. Because collagen type III is present in the fibrous plaques of Peyronie's Disease as well as in the normal tunical tissue, a link between RF therapy and Peyronie's merits further research.[32]

Further randomized sham-controlled studies are essential to verify our preliminary results. In order to define the ideal treatment protocol and the most favorable levels of energy for optimal results.

Conclusions

To our knowledge, this is the first clinical trial on RF treatment for ED published in the english literature. In this pilot study we evaluated a RF energy-based treatment for ED. Its innovation lies in the pioneering use of RF energy for treatment of ED, by employing an innovative handheld, individually operated device specifically designed for home-use. We demonstrated the applicability, safety, and short-term efficacy of this novel self-use device in improving ED. Our preliminary results are promising but still call for multicenter, long-term, randomized and sham-controlled studies to better define its efficacy and to explore the characteristics of the patient who will benefit most from it.

Declarations

Ilan Gruenwald: designed the protocol, participated in executing the study protocol data extraction and evaluation, reviewing and editing the manuscript.

Boaz Appel: designed the protocol, participated in executing the study protocol data extraction and evaluation, reviewing and editing the manuscript.

Arik Shechter: designed the protocol, participated in executing the study protocol data extraction and evaluation, reviewing and editing the manuscript.

Alexander Greenstein: designed the protocol, participated in executing the study protocol data extraction and evaluation, reviewing and editing the manuscript.

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Tables

Table 1 is available in the Supplementary Files section.

Figures

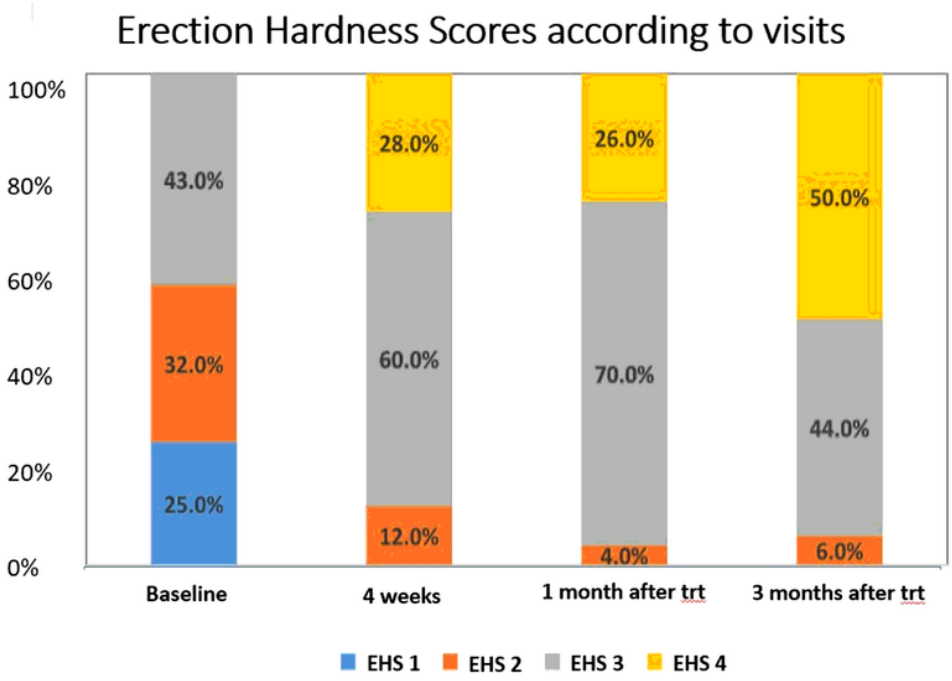
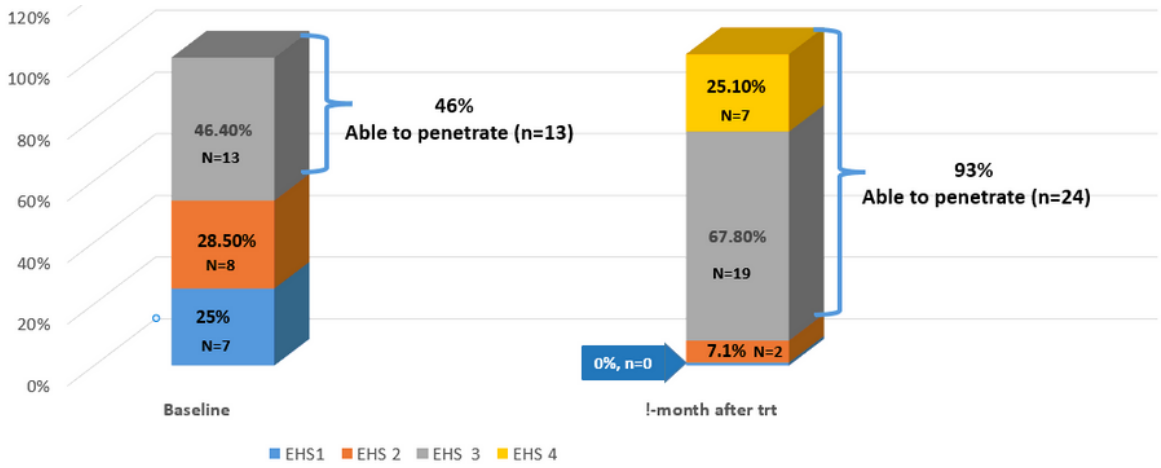
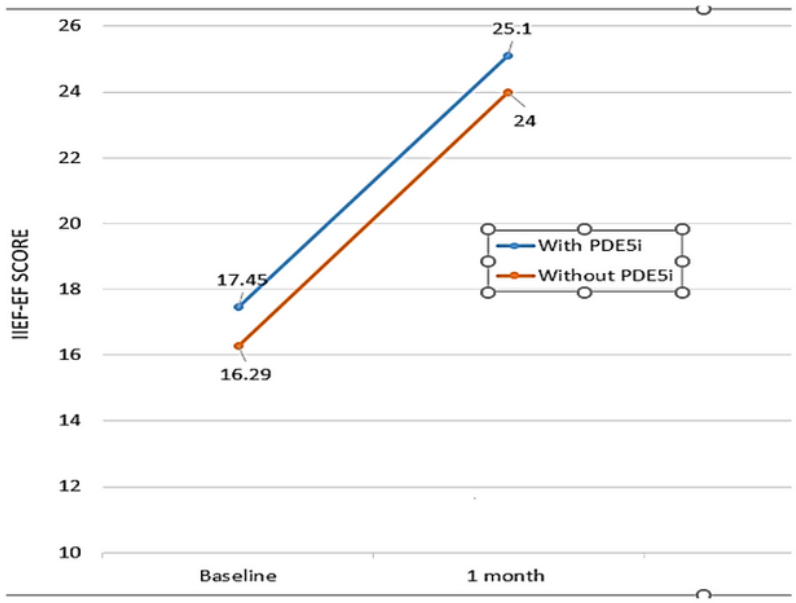


Figure 1

Erection Hardness Scores according to visits





p=0.005

P<0.001

Figure 2

IIEF-EF scores in the PDE5i's treated and non-treated groups

Figure 3

Vertica® front view

Figure 4

Vertica® rear view

Figure 5

Vertica® User panel

Figure 6

Vertica®: Ring and Pad

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- RFtable126..1.23.docx