Peer Review File

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Reviewer A

Nicely written retrospective review evaluating the use of SWT for ED, comparing two different modalities. Total number of patients is small between each group and this study is limited by its retrospective nature.

A few questions for clarification:

1) Do you have longer follow-up for patients that were treated in 2017. Could you add long-term follow-up for those patients, I think that would make the durability of both treatments more transparent. 6 weeks is okay, but given some patients were treated years ago, hopefully there is additional data for those.

Reply 1: We agree that long-term follow-up would enhance this retrospective study. Unfortunately, we do not have longer-term data as our patient population is largely composed of out-of-town referrals who subsequently follow with their local urologists or primary care physicians if they are doing well.

Changes in the text: None

2) You did not discuss side effects or complications of treatment. Many studies suggest that it is safe, but this was not specifically discussed. Is there a difference between the two modalities?

Reply 2: Thank you for pointing this out. We note at the end of the results section, page 11 line 203, that none of the patients in this study experienced a reportable adverse effect. Additionally, we added a statement on the side effect profiles of both modalities in the discussion section.

Changes in the text: lines 280-281, page 12 “Side effects of both fSWT and rWT are minimal and short-term, including bruising, swelling, paresthesia, or pain in the treatment area (Roerdink et al).”

3) In the rWT group 25% had no improvement, but in the fSWT 46% had no improvement. Would this not suggest that rWT is more likely to provide improvement, but fSWT offers greater improvement? IE: the change was not statistically significant, but those that did change would need to have a greater improvement to account of those that did not receive benefit. It would be nice to see what the total change is for those that had improvement, excluding those that had no improvement.

Reply 3: We agree that subset analysis would be of value. Among the 13 patients in the fSWT arm who saw any benefit (grade 2 or 3 response), the mean change in SHIM was 10.0. Among

the 18 patients in the rWT arm who saw a benefit, the mean change in SHIM was 8.72 ($p = 0.35$). As you suggested, on first look the fSWT arm did appear to have a greater change in SHIM among those who experienced any benefit, however it was not statistically significant and due to the small sample size made smaller by subgroup analysis, we hesitate to draw any conclusions from this and therefore opted not to include this subgroup analysis in pilot study.
Changes in the text: None

4) Are there any factors that predict failure / no improvement?
Reply 4: Due to the limited sample size of this pilot study, our analyses for predicting failure yielded no purposeful results. We agree that studies with larger sample sizes should be carried out based on the preliminary results of our pilot study to interrogate this question.
Changes in the text: None

Reviewer B
This is an interesting retrospective study entitled "Retrospective comparison of shock wave therapy and radial wave therapy for men with erectile dysfunction". The authors evaluated the results after the focused (fSWT) and radial (rSWT) SWT. We have seen many studies showing some improvement in erectile function (EF) with SWT in the past few years. However, there are many different protocols and devices, which leads to a high heterogeneity in relation to the results with SWT. One of the main problems is about the source of shock waves, as well as exposed by the authors in this study, comparing two types of SWT.

However, I have some important points to discuss about this study.

MAJOR CONCERNS
1. The main issue of this study is the sampling of the patients included. First, the authors stated that they included all men treated for erectile dysfunction (ED) in their institution between 2017 and 2019. Then, they found exactly the same number of patients in both arms - 24 patients. This is very interesting, as this is a retrospective study. If the authors performed a matched comparison to control confounding factors between the arms, this should be explained in the methodology section. Two very similar arms, based on a retrospective study, are quite unusual.
Reply 1: The first device we acquired and utilized was the UroGold 100 focused shockwave machine. Our Zimmer enPuls radial wave therapy machine was acquired some time later. As a result, the volume of patients treated by focused shockwave therapy was initially much greater. However, due to practice logistics and geography, the radial wave therapy machine was utilized more frequently than the focused shockwave device, and the number of patients treated by each quickly equalized. By keeping a loose eye on the number of patients treated by each modality

we knew when the number treated by each was similar and opted to compare the two treatment modalities when they reached a similar patient volume. All data were collected in a retrospective manner, no patient matching was utilized, and no a priori, prospective patient selection was performed. The similarity in baseline characteristics between the two groups is coincidental and likely reflects the select group of patients we recommend undergo SWT. The study population was not all ED patients, rather it was patients offered SWT outside of study protocols. We clarified this point in the Methods section.
Changes in the text: Page 8 line 170-172: “We performed an IRB approved retrospective review of all men with ED that were treated with either fSWT or rWT *outside of other existing SWT research protocols* between 2017 and 2019 at our institution in two clinical locations.”

2. The other issue related to sampling is the small number of patients in each arm. Probably, the authors did not consider any difference between the arms in relation to those that reached grade 2 due to the sample size. However, the number of patients is too small to be able to find a statistical difference between the arms. For example, the authors found 24% (6/24) and 46% (11/24) of patients who reported no improvement in the rSWT and fSWT groups, respectively. Despite this, they found no 'statistically significant difference' between groups. Probably due to the small number of patients in each group. Authors should discuss this limitation in depth in the discussion section, as it reduces the ability to compare groups and, consequently, their conclusion. In addition, because the self-reported rate of improvement of grade 2 or greater is the primary objective of the study.
Reply 2: We agree that more elaboration on this crucial limitation is necessary. We have expanded our limitations to explain the limitation of small sample size in our study.
Changes in the text: line 363-368, page 13 “Although 24% (6/24) and 46% (11/24) of patients reported no improvement in the rWT and fSWT groups, respectively, the small number of patients in each arm may have precluded the detection of a statistically significant difference. The findings from this pilot study are unable to provide definitive guidelines of superiority of one technique over another. However, larger studies powered for this analysis may corroborate our findings more definitively.”

3. In the summary, the authors stated that they aimed to "evaluate the efficacy of rSWT and fSWT for ED ...". However, in the manuscript they declared "to evaluate our results with rSWT compared to fSWT". The objective must be the same: to evaluate the effectiveness of the modalities or to compare the effectiveness between the modalities. Despite similar objectives, these are different, since the small sample size reduces the power to compare groups.
Reply 3: Thank you for pointing out this critical difference in wording. We have revised all wording to explain the objective of the study: to compare the effectiveness between the two

modalities.
Changes in the text:
Line 63-64 page 4. “Our objective is to compare the efficacy of rWT and fSWT for ED at our institution.”
Line 164-165, page 8. “The objective of this study is to compare the effectiveness of rWT and fSWT on ED.”

4. Regarding the conclusion, the authors cannot assure readers that rSWT and fSWT do not have a "discernable difference" in the treatment of vasculogenic ED. This should be rewritten in the manuscript completion section and summary for '... similar results were found between the groups in our study, however, further studies with larger samples are needed to confirm our results before any recommendations on this topic '.
Reply 4: This change has been made in the manuscript.
Changes in the text: Line 399-401, page 14.

5. The scenario of patients using PDE5i should be discussed further. Did they use PDE5i on their own or after not getting enough erections for penetration, did their urologist prescribe this medication? This is a potential confounding factor and should be discussed as a limitation.
Reply 5: All men treated with either rWT or fSWT had access to PDE5i, whether it was already available or newly prescribed by the study investigators. Patients who needed PDE5i after SWT and achieved full erections were reported as grade 2 improvement. Those who did not need PDE5i after SWT for full erections were reported as grade 3 improvement. We elaborated on PDE5i as a potential confounder in the discussion.
Changes in the text: Line 207-209 on page 4: “Patients were instructed to try PDE5i if they did not have full erections after SWT. Those who did not already have a supply received a prescription from the study investigators.”

Line 373-393 page 13-14: “The usage of PDE5i is a potential confounding factor that limits the ability to draw conclusions about efficacy of SWT as a stand-alone treatment. However, 8/24 (33%) and 9/24 (37.5%) of men treated with rWT and fSWT, respectively, reported grade 3 improvement not requiring use of PDE5i after SWT, suggesting the independent efficacy of both SWT modalities in a sizable minority of men.”

MINOR CONCERNS
1. In the summary, the authors stated their primary endpoint as self-reported improvement of grade 2 or grater, but this is not clear in the manuscript. This should also be made clear in the methodology section of the manuscript.

Reply 6: We elaborated on this endpoint in the methods section of the manuscript.
Changes in the text: Line 211-212, page 9: “The secondary endpoint is a self-reported improvement of grade 2 or greater.”

2. Please include the reference above in the discussion section on the SWT mechanism.
10.1016 / j.jsxm.2019.12.024
Reply 7: Thank you for pointing out this manuscript. We added a reference to this article in the discussion section.
Changes in the text: Page 12 line 288

3. The authors mentioned that "the use fSWT or rSWT was dictated by clinic location, the patients nor urologist chose which machine they preferred". How exactly was this defined, since the study was of patients from the same institution?
Reply 8: Our institution has multiple hospital sites. Patients were offered the shockwave machine at the site they had their urology appointment at or where they preferred to follow-up based solely on geographic preferences.
Changes in the text: Page 8 lines 173-175. “The use fSWT or rWT was dictated by clinic location where the treatment was administered; the fSWT machine was located at one outpatient clinic location and the rWT machine at another, neither the patients nor the urologist chose the SWT modality.”

Reviewer C
This manuscript compares the therapeutic effects of two shock waves (fSWT and rSWT) on ED.The author has conducted meaningful research, but there are a few points in this manuscript that need to be addressed.
1. Many patients are older. I wonder if they have chronic diseases such as diabetes, or hypertension.
Reply 1: We agree, however the small number of patients in each arm precludes meaningful comparison of chronic conditions between the two groups. We did compare age, which showed no difference.
Changes in the text: None

2. It is necessary to make more comparison and discussion on the effects of the two shock waves on tissues from the perspective of the operating principle of the equipment.
Reply 2: Thank you for pointing this out. We made an effort to compare and contrast the two mechanisms of “shockwave” creation in the introduction section. We discuss mechanistically how the wave forms are created (piezoelectric, electromagnetic, electrohydraulic for fSWT

versus a ballistic projectile striking an endplate for rWT) and how they travel through tissues differently (fSWT penetrates tissue deeper on a targeted focal point versus a dispersive shockwave emitted radially away from the tip of the probe in rWT). This discussion can be found on Page 6, line 109 through page 7, line 158. Additionally, we speak to the proposed mechanism of action with regards to vasculogenic erectile dysfunction in the discussion on page 12, lines 272 – 279. Most of the data on the proposed mechanism of action of SWT in ED is derived from focused shockwaves. The basic science behind rWT is less robust.
Changes in the text: none

3. The results in this paper show that both shock waves are effective. But what's the difference between the two shock waves? What are their strengths and weaknesses?
Reply 3: Focused shockwaves are created by an electrohydraulic, piezoelectric, or electromagnetic energy source. The acoustic energy wave created is reflected such that the shockwaves convene at a focal point some distance from the tip of the probe, effectively focusing the energy experienced by the tissue at the focal point. The advantages of focal shcokwaves include 1) more robust scientific and clinical evidence regarding its mechanism of action and clinical efficacy, 2) it has been the device utilized in all the clinical trials to date that utilize shockwave therapy to treat erectile dysfunction, 3) it has FDA approval (although not to treat erectile dysfunction), and 4) urologists are comfortable with the science of focused shockwave therapy, as this is the technology utilized in extracorporeal shockwave therapy for urolithiasis.

Radial waves are created when a ballistic projectile strikes an endplate, creating a comparatively slow rise and fall of acoustic energy that emanates radially from the tip of the device probe. The depth of tissue penetration is less than what can be achieved with focused shockwaves, though the clinical implications of this difference in erectile dysfunction, where the target tissue is shallow, is unclear. The major disadvantage of radial waves is the paucity of data supporting its use in erectile dysfunction, which is the primary motivation for the study completed herein. The primary advantage of radial waves include its classification as an FDA class 1 device, which does not require regulatory approval for use and does not require medical training for the person administering treatment.
Changes in the text: none