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Safety and Efficacy of Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction: A Systematic Review and Meta-Analysis

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Abstract

Background: Erectile dysfunction is a common disease that has a significant negative impact on the quality of life of individuals. Low-intensity shockwave therapy (LI-ESWT) has been considered a new method for treating patients with erectile dysfunction.
Objectives: To evaluate the safety and efficacy of LI-ESWT in the treatment of patients with erectile dysfunction.
Methods: A systematic review was conducted in the major databases, including PubMed, Cochrane Library, Embase, Scopus, and Web of Science up to February 2018. In order to find more articles, the reference list of the key review articles was searched as well. The quality of the studies was evaluated with the Cochrane Collaboration's tools. The outcomes included The International Index of Erectile Function (IIEF), Erection Hardness Score (EHS), and adverse events. Meta-analysis was performed using RevMan software, version 5.3.
Results: Seven randomized clinical trials involving 519 patients met the inclusion criteria. A significant improvement was observed in IIEF (mean difference [MD] = 4.54, 95% CI 0.44 - 8.63) and EHS (risk ratio [RR] = 2.99, 95% CI 1.16 - 7.70) in the intervention groups compared to the control groups. Sub-analysis showed that shockwave therapy significantly improved IIEF at 6, 9, and 10 weeks after the treatment ($P < 0.05$), and the EHS was improved at 5, 6, and 9 weeks ($P < 0.05$). There was also a significant improvement in the intervention groups in IIEF and EHS for 1500 and 3000 pulses, respectively ($P < 0.05$). No significant side effects were reported.
Conclusions: The findings of this study indicate LI-ESWT improves erectile dysfunction in patients, and it is safe and well-tolerated by patients.

Keywords: Erectile Dysfunction, Shock Waves, Randomized Controlled Trial

1. Background

Erectile dysfunction refers to the inability of a man to maintain an erection sufficient for satisfying sexual activity (1). Erectile dysfunction is a common medical problem in men over 40 years of age. Although it is a benign disorder, it may affect physical, mental, and social health; and ultimately affects the quality of life (2-6). The prevalence of erectile dysfunction in men less than 40 years old is about 1 to 10 percent, and in men 40 to 70 years of age, it is 50 percent (7). It is expected that its prevalence will reach from 152 million people in 1995 to 322 million by 2025 (8). The risk factors for erectile dysfunction include hypertension, dyslipidemia, diabetes mellitus, atherosclerotic heart disease, smoking, low serum testosterone levels, and obesity (9, 10).

The first line of the treatment for erectile dysfunction is phosphodiesterase type 5 inhibitors (PDE5i) and the second line of treatment is the use of intracavernosal injection with vasodilating agents. The clinical effectiveness of these treatments may be up to 70% and have significant safety (11). The PDE5 inhibitors have developed changes in the treatment of patients with erectile dysfunction so that about 60% of patients can improve their erectile function and have satisfactory sexual activity (12, 13). Despite the effectiveness of PDE5 inhibitors in the treatment of erectile dysfunction, 40% to 50% of patients, depending on the cause of the disorder, do not respond to the drug even with methods such as combination therapy (14-17).

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These include patients with intolerance to side effects of inhibitors, those who take nitrates for angina, or patients who are resistant to inhibitors, especially patients with diabetes mellitus and surgery due to membrane nerve injury (mainly owing to radical prostatectomy), which is currently the most common cause of erectile dysfunction (18, 19). In addition, the inhibitors may be used with caution or contraindicated in some patients (20). The use of PDE5 inhibitors in a study significantly increased the risk of malignant melanoma (21).

Although phosphodiesterase inhibitors are currently used as the most extensive treatment for erectile dysfunction, they only treat symptoms of erectile dysfunction and does not cure penile pathologies, such as vascular lesions due to diabetes mellitus, structural lesions secondary to trauma or neurological damage secondary to proctectomy (22). Therefore, the pathogenesis of erectile dysfunction and the discovery of new treatments are very important (23). In the 1980s, shockwave with various intensities was used in medicine. Severe shockwave (450 bar) is used in the treatment of nephrolithiasis (200 bar), arthralgia, tendonitis, and bursitis, and recently, low-intensity shockwave therapy (LISWT) (80 bar) is employed in the treatment of erectile dysfunction (17). It is also used for the treatment of musculoskeletal disorders (24), myocardial infarction (25), and untreatable ulcers (26).

The US Food and Drug Administration (FDA) first approved the shockwave device for the treatment of proximal plantar inflammation in 2000, and confirmed this procedure for treating elbow in 2002. Shockwave therapy is a new, non-invasive, non-surgical treatment without the risks of surgery, whose clinical applications have been constantly increasing over the years (27). In recent years, low-intensity extracorporeal shockwave therapy has been shown to be a therapeutic option in the treatment of men with sexual dysfunction; however, its molecular and cellular mechanisms remain unknown (28-30). In order to use and apply a new, non-pharmacological, and non-invasive treatment in patients with erectile dysfunction, it is necessary to carefully collect the clinical data in order to evaluate the safety and efficacy of the new method. On the other hand, the clinical trials on the use of shockwave therapy for the treatment of erectile dysfunction were performed in a short duration and on a small scale.

2. Objectives

This study aimed at evaluating the efficacy and safety of shockwave therapy in the treatment of patients with erectile dysfunction.

3. Methods

We used PRISMA as a guideline for the preparation and reporting of our systematic review and meta-analysis (31).

3.1. Literature Search Strategy

A systematic search was conducted in electronic databases, including PubMed, Embase, Scopus, Web of Science, and Cochrane Library until February 2018. In order to find further evidence, the reference list of review studies and studies related to the subject, as well as key journals in this field were manually searched. Unpublished studies and conference articles were searched at Open Gray, ClinicalTrialgov, and EU CTR. In our search, the year of the publication and language were not considered.

3.2. The Inclusion and Exclusion Criteria

Published studies were selected for analysis based on the following criteria:

(1) published in English, (2) study population: patients with erectile dysfunction, (3) intervention: LI-ESWT, (4) comparison: placebo, (5) outcome: the international index of erectile disease (IIEF) and erection hardness score (EHS), and (6) study design: a randomized clinical trial. The exclusion criteria were the studies conducted on erectile dysfunction along with other illnesses, those examining unrelated outcomes, cohort and retrospective studies, case reports, letter to editors, and so on.

3.3. Study Selection and Appraisal

After removing duplicates, the two authors independently reviewed the titles and abstracts based on the criteria. Discrepancies were resolved through discussions between the two authors. In case of disagreement, a third person entered the discussion. The quality of randomized clinical trial was evaluated using the Cochrane Collaboration's tools by the two authors.

3.4. Data Collection and Extraction

The two authors separately extracted data using a constructed data extraction form. The extracted data included the characteristics of the study (design, duration, and follow-up duration), characteristics of the participants (age and number of patients), interventions (number and duration of the treatment with intervention), measured outcomes and side effects. After completing the data extraction forms, the differences were discussed and finalized by the two authors. Eventually, the efficacy and safety outcomes were analyzed.

3.5. Data Analysis

Efficacy and safety outcomes, including IIEF, EHS, and adverse events, were analyzed. In order to investigate the heterogeneity between the studies, I2 index and chi-square test were used. The random or fixed effect model was used to calculate effect size based on the heterogeneity of the studies. In order to analyze the obtained data, a meta-analysis was performed using RevMan software, version 5.3.

4. Results

4.1. Characteristics of the Studies

Figure 1 shows the search process, exclusion of duplicates, and screening based on title, abstract, and full text. After deleting duplicates, 671 articles remained, which were independently reviewed based on title, abstract, and full text by the two authors. Discrepancies were resolved via conversation. A total of 84 studies were eligible for full-text review. Finally, seven studies (19, 28, 29, 32-35) were eligible for inclusion in the study. The studies were published between 2010 and 2017. The characteristics of the studies are presented in Table 1. Also, the quality of the studies and the risk of bias were evaluated using the Cochrane Collaboration's tool for assessing the risk of bias (Figure 2).

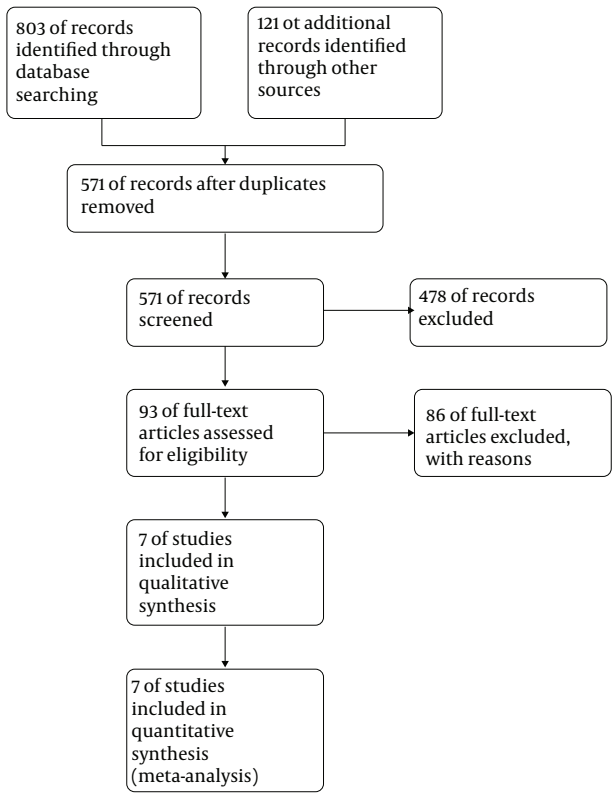

Figure 1. Represents the study flow diagram (PRISMA)

4.2. Efficacy Outcomes

4.2.1. IIEF

The total mean difference was 4.54 (MD = 4.54, 95% CI 0.44 - 8.63), which indicates that shockwave improved IIEF compared to the placebo (Figure 3A). Also, the mean difference of 6, 9, and 10 weeks for shockwave therapy compared to placebo was 6.92 (MD = 6.92, 95% CI 2.51 - 11.31), 2.74 (MD = 2.74, 95% CI 0.28 - 5.19), and 0.7 (MD = 0.7, 95% CI 0.24 - 1.16), respectively. Accordingly, the highest improvement in IIEF was observed at 6 weeks after the treatment (Figure 3B). The total mean difference of 600, 1500, and 300 pulses/treatment was respectively 2.05, 4.1, and 11.1, respectively. For 600 pulses/treatment, there was no significant difference between shockwave therapy and control ($P > 0.05$), while for 1500 and 3000 pulses/treatment, it was significant ($P < 0.05$) (Figure 3C).

4.2.2. EHS

The risk-adjusted value was 2.99 (RR = 2.99, 95% CI 1.16 - 7.70), indicating shockwave therapy significantly improved patients' scores in comparison to the control (Figure 4A). The relative risk ratio of 5, 6, and 9 weeks was 6.14, 25.71, 1.7, and 0.52, respectively ($P < 0.05$), but it was not significant for 10 weeks ($P > 0.05$). The greatest improvement was observed for 6 weeks after the treatment (RR = 25.71, 95% CI 3.71 - 178.80) (Figure 4B). The relative risk ratio of 600, 1500, and 300 pulses/treatment was 0.52, 2.14, and 9.67, respectively. For 600 and 1500 pulses, there was no significant difference between the shockwave therapy and control ($P > 0.05$), but for 3000 pulses, it was significant ($P < 0.05$) (Figure 4C).

4.3. Safety Outcomes

Significant side effects were not reported for patients during and after the treatment with shockwave therapy. The treatment was completely safe and well-tolerated by all patients. The only cases mentioned in the studies were pruritus (34) and minor burning sensation (29) that did not require treatment. In other studies, side effects were not reported by patients.

5. Discussion

The purpose of this systematic review and meta-analysis was to examine LISWT in the treatment of patients with erectile dysfunction. Seven randomized clinical trials

Table 1. Characteristics of the Included Clinical Trials

First Author	Year	Country	No.	No. of Patients		Total Number of Treatments	Number of Treatment/Week	Pulse/ Treatment	Energy Ddensity, mJ/mm^2, PPM	Follow-up, mo
				Treatment	Control					
Fojecki (34)	2017	Denmark	126	63	63	10	1	600	0.09	2, 4
Kalyvianakis (35)	2017	Greece	46	30	60	6	2	600	0.09	1, 3, 6, 9, 12
Kitrey (33)	2016	Israel	58	40	18	6	2	1500	0.09	1
Olsen (29)	2015	Denmark	105	51	54	5	1	3000	0.15	1, 3, 6
Srini (32)	2015	India	135	95	40	6	2	3000	0.09	1, 3, 6, 9, 12
Vardi (19)	2012	Israel	67	46	21	9	2	1500	0.09	1
Yee (28)	2015	China	58	30	28	9	2	1500	0.09	1

have evaluated the efficacy and safety of shockwave therapy compared to placebo in the treatment of patients with erectile dysfunction. Numerous studies used standard indicators of IIEF and EHS to measure the efficacy outcomes. The results of the meta-analysis showed that shockwave therapy improved the IIEF and EHS indices in patients with erectile dysfunction compared to the controls. The published review articles showed that shockwave therapy is an effective treatment in patients with erectile dysfunction, which confirms the findings of this study (36, 37).

The idea of using shock-wave therapy for male genitalia belongs to an animal study that proved shockwave energy to pig's myocardium reduced myocardial dysfunction due to ischemia. Although the mechanism of action has not yet been described, it can be assumed that the shock applied on the penis can increase blood flow and improve endothelial function by stimulating angiogenesis in the cavernous hemangioma (17). Shockwave therapy has been used in the last decade as a new treatment for patients with erectile dysfunction, and clinical studies and reports have been particularly focused on this topic, especially over the past five years (36).

The primary goal in the management strategy for patients with erectile dysfunction is to determine the cause and treatment (4). Management of erectile dysfunction includes PDE5 inhibitors, vacuum constriction devices, intracavernosal injection, penile prosthesis, and so on (38).

The European Urology Association has recommended the use of PDE5 inhibitors such as Sildenafil, Tadalafil, Vardenafil, and Avanafil as the first-line oral treatment for patients with erectile dysfunction. The latest guideline published by the European Urology Association recommends that PDE5 inhibitors provide an effective and safe treatment for erectile dysfunction. Although data are still limited and inadequate in terms of the impact of shockwave therapy, there is no recommendation on the use of this technology in patients with erectile dysfunction (39). Subanalysis of the results showed that shockwave therapy with 600 pulses was not effective on IIEF and EHS. But at 1,500 and 3,000 pulses, it improved IIEF, and at 3000 pulses, it improved the EHS. In the study by Zhihua (35), meta-analysis results showed that shockwave therapy with 3000 pulses per treatment caused more improvement in comparison to 1500 or 2000 pulses per treatment, which is consistent with the results of the present study. It seems that by increasing the number of pulses, there is greater effectiveness in improving IIEF and EHS.

Also, shockwave therapy for 5, 6, and 9 weeks was associated with an improvement in IIEF and EHS, and the highest improvement in IIEF and EHS was observed in the 6th week. In the study of Lu et al. no significant improvement was observed in IIEF after one month, but a significant enhancement was observed in IIEF after three months (36). Other published review studies have shown that shockwave therapy for other conditions, such as chronic wounds, acute and chronic soft-tissue wounds (40), orthopedic conditions (41), common lower limb conditions (42), acute trauma (43), and intermittent claudication (44), can be effective. However, in a meta-analysis study published in 2016, no significant difference in pain symptom improvement was observed for shockwave therapy compared to other methods or controls (45). The author stated that higher quality evidence is required to make a decision regarding this issue (45). Although our study shows that shockwave therapy is effective and safe in treating patients with erectile dysfunction, the FDA has not yet approved the technology for treating patients with this condition. Also, according to the latest guideline published by the American Urology Association in 2018, the level of evidence for the use of shockwave therapy to treat men with erectile dysfunction is at the C level (38).

5.1. Conclusions

The findings of this meta-analysis showed that shockwave therapy is an effective, safe, and minimally invasive option for patients with erectile dysfunction, which improves this condition without side-effects, but further studies on this issue are warranted.

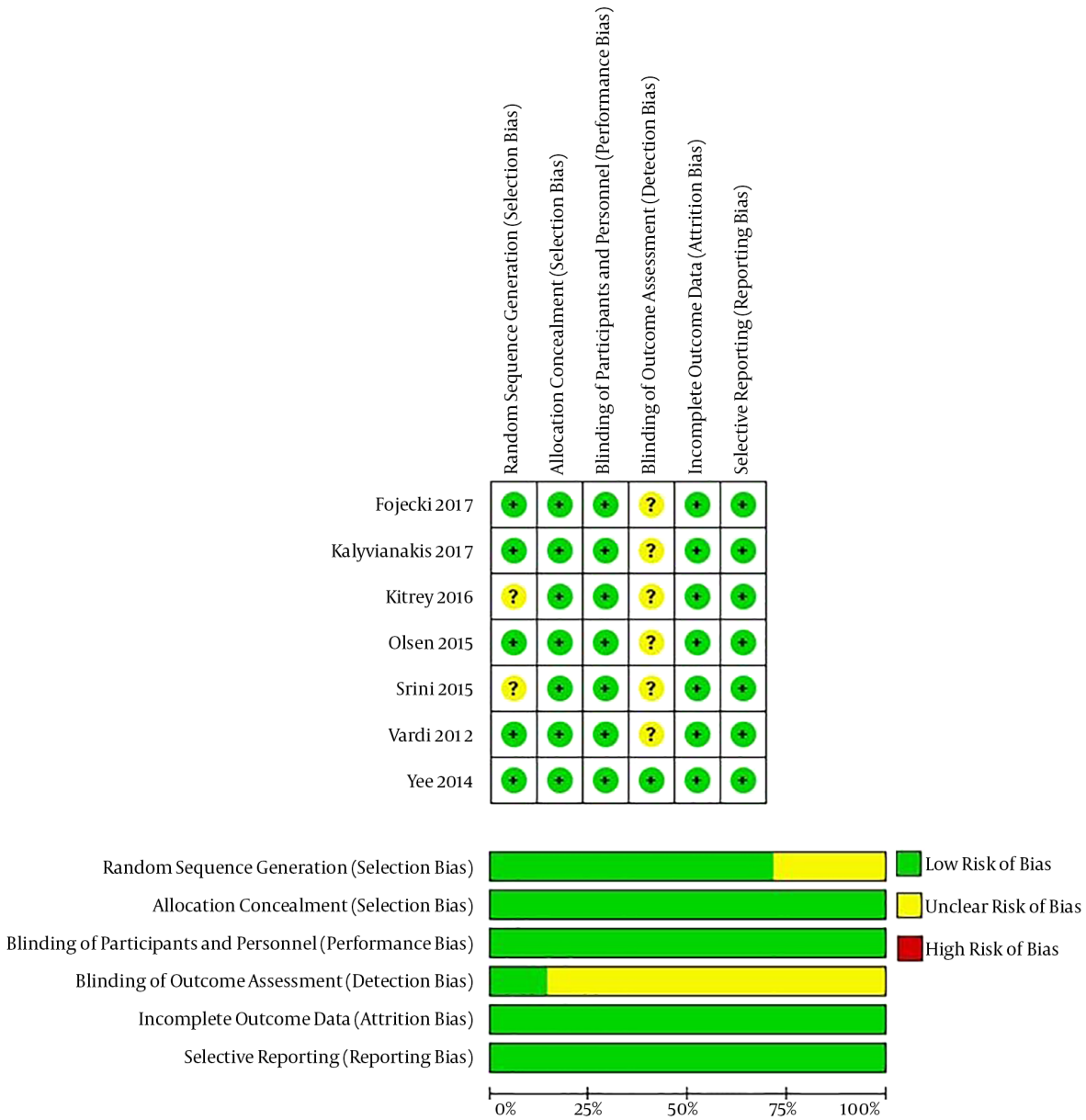

Figure 2. The risk of bias graph is shown

Footnotes

Authors' Contribution: Study concept and design: Nabi Shariatifar and Farhad Azadi; literature searching: Bahman Amani, and Roohallah Shabestan; study selection and appraisal: Bahman Amani, and Nabi Shariatifar; data collection and extraction: Behnam Amani and Roohallah Shabestan; data analysis: Bahman Amani and Arash Akbarzadeh; all authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflict of Interests: There are no financial conflict of interests to disclose.

Ethical Considerations: Since our study does not involve human subjects, there is no ethical consideration.

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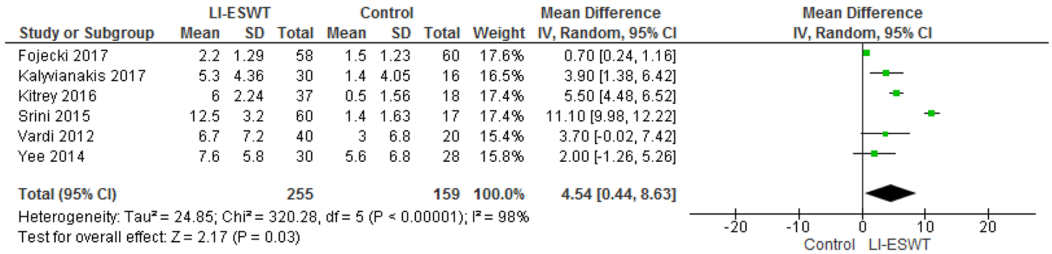
A



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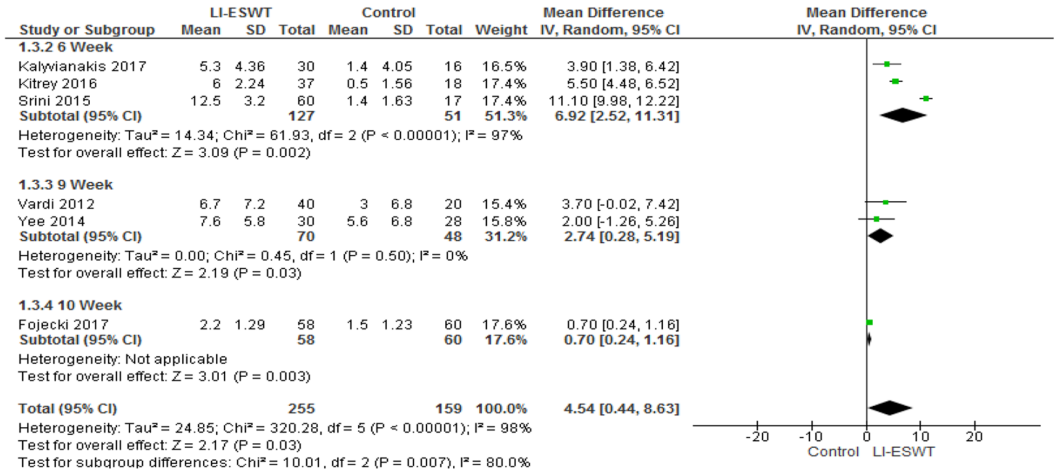

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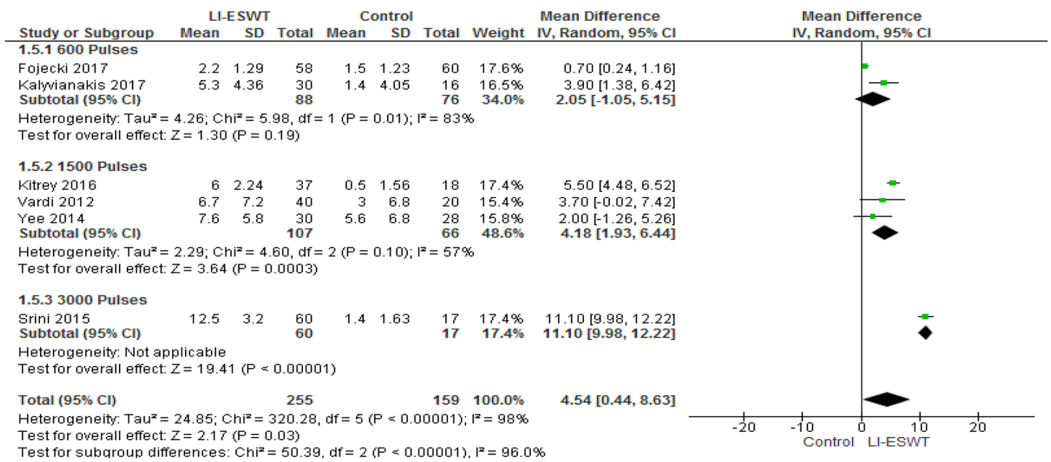
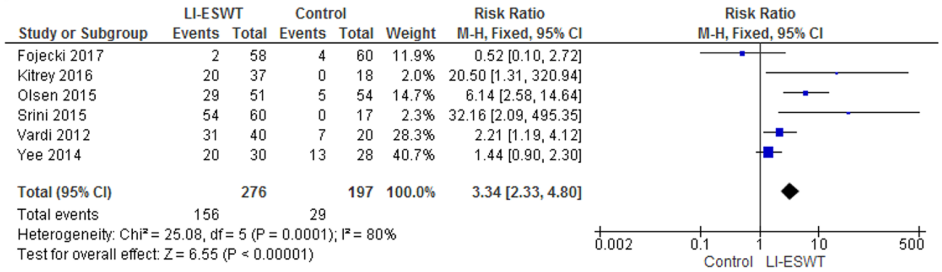


Figure 3. Pooled MD of efficacy outcomes based on IIEF score (A), the treatment duration (B), and shocks per treatment (C)

A



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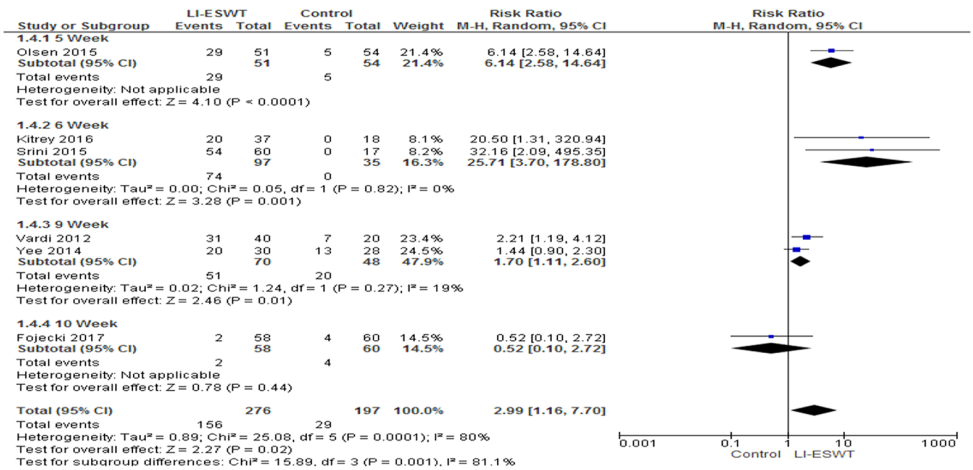

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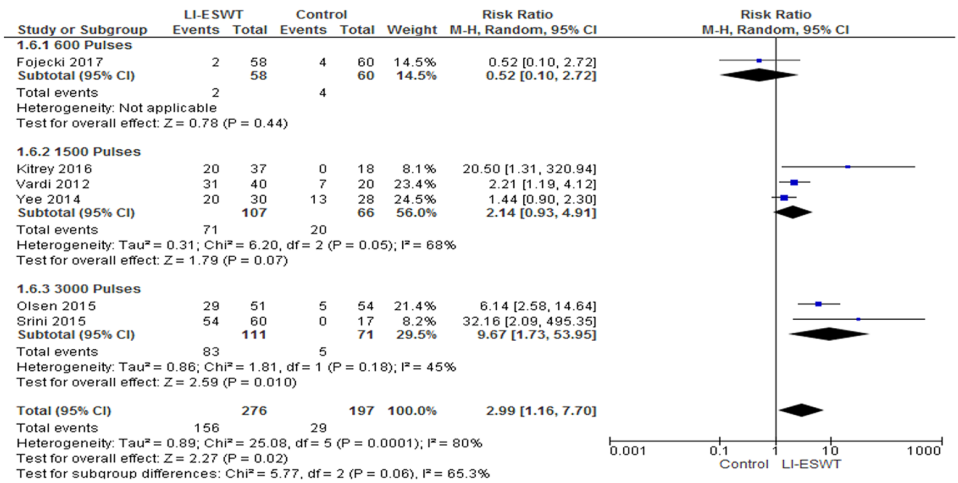

Figure 4. Pooled RR of efficacy outcomes based on EHS (A), the treatment duration (B) and shocks per treatment (C)

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