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Therapeutic Approach to Erectile Dysfunction - News and Future Perspectives

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Abstract

Erectile dysfunction is defined as the inability to get or keep an erection that is sufficient for satisfactory sexual intercourse. It is one of the most prevalent sexual dysfunctions in men, usually correlated with aging. This pathology is generally associated with repercussions in the psychological and social well-being of the patient and his relationship with his partner. This way, it is considered an important cause of a decrease in quality of life. The treatments available today, in most cases, solve the symptoms, however, none of them can reverse the physiopathological basis of erectile dysfunction. In addition to that, they can also interfere with the spontaneity of sexual intercourse, which may be an obstacle to their use. The search for new therapeutic alternatives for erectile dysfunction is in constant development. As sexuality is an important element in human life, an update on these therapeutic advances becomes pertinent, since they could eventually change the paradigm of treatment of this pathology. This work aims to produce a review of the evidence on recent therapeutic advances in erectile dysfunction, as low-intensity shockwave therapy, botulinum toxin treatment, and platelet-rich plasma therapy. This way, a wide bibliography research will be conducted, through online databases and relevant manuscripts.

Keywords: Therapeutic; Dysfunction; Erectile

Abbreviations: ED: Erectile Dysfunction; LiSWT: Low-Intensity Shockwave Therapy; PRP: Platelet-Rich Plasma Therapy; NO: Nitric Oxide.

Introduction

Erectile Dysfunction (ED) is the inability to achieve or maintain an erection for satisfactory sexual performance; it is one of the most prevalent sexual disorders in males. This pathology is generally associated with negative repercussions on the psychological and social well-being of men as well as on the relationship with the partner, thus being considered an important cause of decreased quality of life [1-4].

Treatment of ED has the primary objective of enabling couple a satisfactory sexual experience. The modification of the various lifestyle factors that are frequently associated with ED, such as smoking, alcohol consumption, obesity and physical inactivity, has considerable effects on improving ED. Thus, the adoption of lifestyles that improve vascular function is recommended in all men with ED.

Phosphodiesterase 5 inhibitors (iPDE5) are used as first-line therapy for individuals who do not have any contraindications to taking it. Although the appearance of these drugs has revolutionized the therapeutic approach to ED, about 35% of patients are refractory to this treatment. The vacuum erection device is also considered a first-line

method, especially in older patients. This device has high efficacy rates; however, satisfaction rates are very variable, and it is estimated that its use will be discontinued in about 50 to 64% of cases. In patients who do not respond to first-line treatments, intracavernous injection of vasoactive drugs is an option. Despite effectiveness rate being around 70%, the complexity of administration and the penile pain that exists after the injection are responsible for the high rate of abandonment in the first months of treatment. Intraurethral pharmacotherapy, although less effective, is an alternative to intracavernous injections, in patients who prefer a less invasive treatment. Finally, surgery with penile prosthesis placement is a third-line treatment for ED. Surgical intervention is usually reserved for patients who do not respond to previous therapeutic modalities or those who want a permanent solution [5,6].

Although strategies currently available for the treatment of ED achieve, in most cases, a reduction in symptoms, they seem to be far from meeting modern needs. None of the previously mentioned treatments is able to reverse the pathophysiological basis of erectile dysfunction; the search for a cure that will allow the restoration of natural erections remains. On the other hand, the existence of population groups that do not respond to first-line treatments, either due to the presence of underlying conditions such as diabetes or due to the impairment of erectile tissue after prostatectomy, are a difficult problem to overcome. A therapeutic method to convert patients that were refractory to iPDE5 treatment into responders is highly sought after. In addition, in most current treatments, the need for on-demand use interferes with the spontaneity of the sexual act, a situation that can be embarrassing, both for the patient and for the spouse [7].

Thus, it is not surprising that the search for new treatments for ED, which on one hand are able to meet the needs of today's society and which and on the other hand, mitigate the obstacles imposed by the current options, has become an emerging practice in the field. Uro-andrological.

The main objective of this work is to conduct a review of the accumulated evidence about the treatment modalities that have recently emerged for ED, namely, low-intensity shockwave therapy (LiSWT), botulinum toxin therapy and platelet-rich plasma therapy (PRP).

Methods

To elaborate this work, an extensive review of the available literature was carried out, using mainly the following databases: PubMED, ScienceDirect, European Association of Urology and Journal of Sexual Medicine. The ClinicalTrials.gov database was used to search for ongoing clinical trials.

The research was conducted in English, using a free text protocol and included, mainly, the following terms: "erectile dysfunction", "treatment", "low intensity shockwave therapy ", "platelet rich plasma" and "botulinum toxin".

Results

Low-Intensity Shock Wave Therapy (LiSWT)

Energy associated with shock waves has had several applications in the various branches of medicine, namely in urology, where it was introduced as a non-invasive therapeutic modality for renal lithiasis. In 2010, Vardi, et al. proposed the use of LiSWT as a new therapeutic modality for ED. Since then, this therapy has been performed on men with ED, on an outpatient basis, without the need for analgesia; the supply of shock waves to the penile tissue is carried out through a probe, using a coupling gel [8-10].

Shock waves used in LiSWT are produced using three different types of energy sources: electro-hydraulic, electromagnetic and piezoelectric. Recently, several companies have started to market devices called "linear shock wave generators"; these devices provide energy to a larger tissue area and are designed to adapt specifically to more linear tissues, such as the penis [11].

The mechanism by which LiSWT influences ED is not yet fully understood. Studies in animal models show that LiSWT appears to improve erectile function, by inducing angiogenesis and reversing some of the pathological processes underlying erectile tissue. It is believed that one of the main mechanisms responsible for neoangiogenesis, which is observed after the application of shock waves, involves the up-regulation of growth factors, especially VEGF. Another presumptive mechanism comprises the recruitment of stem cells and endothelial progenitor cells, which play a major role in the formation of new blood vessels. Studies in animal models show that shock waves induce the up-regulation of stromal cell-derived factor 1 (SDF-1); this factor specifically binds to CXCR-4, which is expressed, essentially, in endothelial progenitor cells and hematopoietic stem cells, playing a crucial role, both in recruitment and in the function of these cells. LiSWT also seems to stimulate vasodilation, with the hypothesis that this therapeutic modality may interfere with the production of nitric oxide (NO) or other vasodilators. Currently, there are few studies that investigate the effects of LiSWT on nerve regeneration, however, it has been suggested that it promotes the removal of degenerated axons and increases the regenerative capacity of damaged axons [7,12].

In 2010, the first study in this area was presented and, since then, number of publications has grown, almost

exponentially. Results of some of the clinical studies published in this area are outlined in Table 1.

Since results of these studies are divergent, several Meta-analyze were published, in an attempt to reach a more definitive conclusion about the effectiveness of LiSWT in vasculogenic ED.

Study	Sample	Therapeutic protocol	Results	Side Efects
Vardi, et al. [13]	60 men with response to iPDE5;	2 sessions/week, for 3 weeks, repeated after 3 weeks; Omnispec ED1000; 0.09 mJ/mm2; 120 shocks /min; 1500 shocks/session distributed over 5 therapeutic points;	IIEF-ED: average increase of 6.7 ± 0.9 in the TG vs. 3.0 ± 1.4 in the PG; Penile endothelial function (ml/min/dl): change in basal blood flow was 4.6 in TG vs. 0.2 in the PG; change in maximal blood flow after ischemia was 8.2 in TG vs. -0.1 in the PG; EHS: 69% of TG patients who initially had EHS ≤2 went to ≥3, vs. 0% in the PG;	
Olsen, et al. [14]	105 men with response to iPDE5;	1 session/week over 5 weeks; Duolith SD1; 0.15 mJ/mm2; 5 Hz; 3000 shocks/session, distributed over 6 therapeutic points;	IIEF-ED: there were no statistically significant differences between the TG and the PG; EHS: 57% of TG patients who initially had EHS ≤2 went to ≥3, vs. 9% in the PG;	Burning sensation
Kalyvianakis, et al. [15]	46 men with response to iPDE5;	2 sessions/week, for 3 weeks, repeated after 3 weeks; Omnispec ED1000; 0.09 mJ/mm2; 160 shocks /min; 1500 shocks/session, distributed over 5 therapeutic points;	Penile hemodynamics: the mean peak systolic velocity (cm/s) increased from 31.11 ± 3.23 to 35.57 ± 3.60 in the TG and from 30.7 ± 3.55 to 31.1 ± 3.50 in the PG; average change of 4.5 cm/s and 0.6 cm/s, respectively;	-
Fojecki, et al. [16]	126 men with and without response to iPDE5;	1 sessions/week, for 5 weeks, repeated after 4 weeks;Piezowave2; 0.09 mJ/mm2; 5 Hz; 600 shocks/session, distributed over 3 therapeutic points;	IIEF-ED: there were no statistically significant differences between the TG and the PG	Local irritation
Kitrey, et al. [17]	55 men refractory to iPDE5 therapy;	2 sessions/week, for 3 weeks, repeated after 3 weeks; Omnispec ED1000; 0.09 mJ/mm2; 120 shocks /min; 1500 shocks/session, distributed over 5 therapeutic points;	IIEF-ED: the median increased from 7 to 13 in the TG and from 8 to 8.5 in the PG; 40.5% of TG men responded to iPDE5 vs. 0% of PG men; EHS: 54.1% of TG patients who initially had EHS ≤2 went to ≥3, vs. 0% in the PG; Penile endothelial function (ml/min/dl): the median change in the post-ischemic time-flow penile was 152 in the TG and -8 in the PG;	

Table 1: Summary of randomized controlled trial related to LiSWT in men with vascular ED. PG: placebo group; PT: treatment group.

In 2017, a meta-analysis, conducted by Clavijo, et al. Analyzed randomized, placebo-controlled clinical trials that used the International Index of Erectile Function - Erectile Function Domain (IIEF-ED) score as a tool for evaluating results. Data were obtained from 7 studies and involved a total of 602 participants with an average age of 60.7 years; the average follow-up was 19.8 weeks. The authors found, in men treated with LiSWT, a statistically significant improvement in the IIEF-ED score, compared to those who received simulated therapy (6.40 points vs. 1.65 points). The average difference in the IIEF-ED score, between the treatment group and the placebo group, was 4.17 points. This meta-analysis demonstrated that LiSWT results in a significant increase in the IIEF-ED score, however Clavijo, et al. emphasize that

careful selection of candidates is crucial for enhancing the benefits of this treatment. The results of two of the clinical trials included in this meta-analysis showed that variables such as: advanced age, presence of medical comorbidities, long-term ED, low baseline IIEF-ED score and a poor initial response to treatment with iPDE5, impair the effectiveness of LiSWT [18].

Likewise, in another meta-analysis, dated 2017 Lu, et al. found that LiSWT significantly improves the IIEF score; the authors found an average difference between the treatment group and the placebo group of 2.00 points. In addition, this meta-analysis showed that severity of ED has an influence on the effectiveness of LiSWT; Lu, et al. Demonstrated that patients with mild ED have a more significant response to LiSWT than those with more severe ED [19].

Finally, a meta-analysis, published in 2018, corroborates the therapeutic benefit of LiSWT in ED. Man, et al. found an average difference in the IIEF score between the treatment group and the placebo group of 2.54 points. In addition, they found that combination of LiSWT with iPDE5 is associated with better results in erectile function, than the application of LiSWT alone. Surprisingly, Man, et al. also demonstrated that shock waves produced by different devices have different effects on IIEF score (Omnispec ED1000, mean difference: 4.14 vs. Duolith SD1, mean difference: 2.7). This meta-analysis also showed that the use of different LiSWT configuration parameters, namely, the density of energy flow, the number of shocks applied per session and the total duration of treatment, results in differences in reported efficacy. The authors revealed that courses of treatment lasting less than 6 weeks are associated with better results in erectile function. Likewise, the use of energy densities in the order of 0.09 mJ/mm^2 and the administration of a greater number of shocks per session (3000 shocks/session) also results in better therapeutic efficacy [20].

ED post-radical prostatectomy is a current problem that is difficult to overcome; these patients are particularly difficult to treat. The incidence rate of ED secondary to prostatectomy is between 6 and 68%; studies shows that, even under treatment with iPDE5, less than half of men return to their baseline level of erectile function. LiSWT's ability to restore erectile function in men with post-prostatectomy ED has been suggested by several experimental studies, which demonstrate that this treatment, in addition to stimulating neoangiogenesis, promotes pro-neurogenic changes, such as the activation of Schwann cells, synthesis of neurotrophic factors, as well as the recruitment and activation of stem cells in the cavernous tissue. Despite this, as this subset of patients is excluded in most clinical trials, the effectiveness of LiSWT in men who develop ED after radical prostatectomy remains unclear [21,22].

In 2016, Frey, et al. conducted the first investigation that included this subpopulation of patients. The authors concluded that LiSWT can improve erectile function after radical prostatectomy. However, it does not seem to do so in a clinically meaningful way, since most participants, even after LiSWT, were unable to achieve an erection sufficient for satisfactory sexual performance [23].

Botulinum Toxin (Botox®)

Botulinum toxin, commonly known by its trade name "Botox®", is known for its use in aesthetic medicine, however lately, it has begun to investigate whether its muscle relaxation capacity could be used in the corpora cavernosa to improve penile erections, thus introducing itself as a new treatment modality for ED. Botulinum toxin is produced by Clostridium botulinum; currently, 7 distinct serotypes of this toxin are identified. Most investigations on the potential therapeutic uses of botulinum toxin focus on subtype A botulinum neurotoxin (BoNT-A), the serotype that has the longest duration of action and, therefore, the one that has the greatest clinical interest. BoNT-A is administered via subcutaneous or intramuscular injection in the target area and is available in different commercial formulations; Botox® is the most well-known formulation. In addition to aesthetic medicine, BoNT-A therapy is established in the treatment of many pathologies, namely in pathologies that affect smooth muscle and striated muscle [24,25].

The mechanism of action of Botox® is already well understood: Botox®, at the cholinergic presynaptic terminals, prevents the fusion of the synaptic vesicle with the presynaptic membrane and, consequently, prevents the release of acetylcholine at the neuromuscular junction, causing relaxation of musculature. Duration of this effect in the striated muscle is between 2-3 months; in the smooth muscle, it is believed that this duration is higher with estimates that point to a duration that can reach up to 12 months [24].

Once that Botox® is a strong inducer of muscle relaxation, and taking into account that the relaxation of the cavernous smooth muscle is an integral part of the development of an erection, in recent years studies conducted in animals and humans have suggested a possible role of intracavernous injection of BoNT-A in treatment of ED.

De Young, et al. performed an study in animals and found that the group treated with BoNT-A showed significantly higher intracavernous pressure when compared to the control group (79.06 ± 5.4 cmH2O vs. 54.26 ± 4.5 cmH2O). In addition, after analyzing the penile tissue histologically, the authors recorded a greater sinusoidal volume in the treatment group, compared to the control group; however,

given the small size of the groups, this difference did not reach statistical significance [26].

Another study, also carried out on animal models, was conducted by a group of Egyptian researchers. As already suggested by the study by De Young, et al. Histological analysis of the penile tissue revealed a significantly greater mean sinusoidal diameter in the treatment groups compared to the control group [24].

Currently, only the results of 2 studies in humans are available. A phase I clinical trial involved 24 men with severe vasculogenic ED, refractory a treatment with iPDE5 and a second-line treatments. Patients were divided into 2 groups: a treatment group (n=12) and a control group (n=12). Both groups received an intracavernous injection of trimix solution (20 µg alprostadil + 1 mg phentolamine + 30 mg papaverine). The next day, the treatment group received 50 units of BoNT-A, while the control group received 1mL of intracavernous saline. In men treated with BoNT-A, there was a statistically significant improvement in vascular parameters; the mean peak systolic velocity increased from 24.6 cm/s to 34.9 cm/s after treatment. Similarly, in the treatment group, there was a statistically significant improvement in the average scores of the Sexual Health Inventory for Men (SHIM) and the Erection Hardness Score (EHS). Of the 12 men who received BoNT-A, 7 (58.3%) were able to have penetrative sexual intercourse with the use of 100 mg of sildenafil; in the control group, only 2 (16.7%) patients achieved identical results. During this study, a man who received BoNT-A had a prolonged erection, which required intracavernous treatment with ephedrine; apart from this, there were no reports of other adverse events, including episodes of priapism or systemic toxicity [24,27].

The second study, a phase II study, was conducted by the same group of researchers in a larger sample of patients, The authors included 70 men with ED refractory to the first 2 lines of treatment; the participants were divided into 2 groups: a treatment group (n = 35) and a control group (n = 35). The methodology applied was similar to that described in the previous study, however, the treatment group, instead of 50 units, received 100 units of BoNT-A. The mean peak systolic velocity of the right and left cavernous artery was assessed, before and after treatment, in both groups. The results were recently released and revealed that, in the group treated with botulinum toxin, the mean peak systolic velocity of the right and left cavernous arteries increased, respectively, from 34.52 cm/s to 45.68 cm/s and from 34.33 cm/s to 46.015 cm/s. In the control group, the mean peak systolic velocity of the right cavernous artery increased from 30.85 cm/s to 31.67 cm/s and that of the left cavernous artery increased from 31.73 cm/s to 32.09 cm/s [28].

Currently, two clinical trials are in the development stage and with no published results so far: NCT03355963 and NCT04172558.

The mechanism by which Botox® influences erectile function is now beginning to be clarified. The presence of sympathetic hyperactivity in erectile tissue, responsible for an increase in vascular smooth muscle tone, is hypothetically involved in the pathophysiology of ED in many patients. Studies in animals have shown an increase in the sinusoidal diameter in the treatment groups, which suggests that BoNT-A induces a relaxation of the cavernous smooth muscle by inhibiting the release of norepinephrine from adrenergic neurons. In this way, the sympathetic basal tone of the cavernous smooth muscle is removed, which facilitates the erection. Once that cholinergic neurons are also inhibited by this treatment, the erection becomes dependent on NO produced from non-adrenergic and non-cholinergic neurons, whose release is independent of the synaptic vesicles and, therefore, is not affected by BoNT-A. The decrease in smooth muscle tone allows an increase in penile blood flow, demonstrated in human studies, by increasing the mean peak systolic velocity [24].

Platelet Rich Plasma (PRP)

PRP is an autologous product whose preparation begins with the collection of the patient's blood, which is centrifuged at different speeds until it's separated into 3 layers: low platelet plasma, PRP and red blood cells. PRP obtained has a platelet concentration that surpasses by 3 to 7 times the physiological standards; in turn, platelets contain several growth factors, such as: the platelet derived growth factor (PDGF), VEGF, fibroblast growth factor (FGF), epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF-1). Platelets play a crucial role in coagulation and in promoting healing, while growth factors are involved in key stages of regenerative processes, namely in the recruitment of stem cells, in the modulation of inflammatory responses and in the stimulation of angiogenesis. Since its introduction in 1987, the medical use of PRP has grown steadily, with reports of its use in the field of orthopedics, otolaryngology, neurosurgery, dermatology, cardiothoracic surgery and, also, in dental medicine. However, the biological properties and effects of PRP in its various clinical applications remain poorly understood [29,30].

Recently, studies have been published that point to a significant role of growth factors in neural regeneration and up-regulation of neuronal NO synthase. This evidence was the starting point for initiating investigations in the uro-andrological field, with the purpose of evaluating the usefulness of the application of PRP in the recovery of erectile function, particularly after injury to the cavernous

nerve [31].

Wu, et al. Published one of the first studies in this area, in which they evaluated the effect of the application of PRP in animal models submitted to cavernous nerve injury. The authors reported a greater preservation of myelinated axons and a significant improvement in erectile function in rats with cavernous nerve damage treated with PRP, compared to the group treated with saline solution. Wu et al. also found that PRP administration resulted in a significant reduction in expression, both of apoptotic markers and of cavernous fibrosis markers. Thus, Wu, et al. believe that growth factors present in the alpha granules of platelets, in addition to acting as accelerators of nerve repair processes, have the ability to inhibit the fibrosis process at the level of the corpora cavernosa [32].

Although animal studies have shown that PRP therapy has the potential to facilitate the recovery of erectile function, at present, there are no robust data that show the safety and viability of this treatment in men with ED.

A study conducted by Matz, et al. in 2018, evaluated the safety and viability of the platelet-enriched fibrin matrix in the treatment of different urological conditions. Each participant received an average of 2.1 intra-lesional injections of PRP. The authors found that this therapeutic modality is well tolerated, safe and viable in patients with ED, Peyronie's disease and stress urinary incontinence. In patients with ED, after application of the platelet-enriched fibrin matrix, an average increase of 4.14 points in the IIEF-5 score was reported. During the 15 months of the study, no adverse effects were observed [33].

Alkhayal, et al. also studied 40 men (mean age: 43 years) with ED, who received intracavernous injections of PRP, according to the protocol established by the American Academy of Cosmetic and Cellular Medicine ("Priapus Shot"). The average score of IIEF-5 at the beginning of the study was 13 and, after treatment, increased to 17. Of the 40 patients studied, 35 (85%) considered that the treatment improved the hardness / firmness of the erection. The follow-up lasted an average of 13 weeks and, during this period, no side effects or deterioration in erectile function were reported [34].

Despite the current lack of clinical evidence to support the effectiveness of PRP in the treatment of ED and the scarcity of plausible biological justifications for its use, this treatment is widely promoted worldwide. PRP therapy is marketed as a "P-shot" or "Priapus shot" in several clinics, most of which are aesthetic, and is advertised on their websites as a treatment method for ED that promises not only to improve sexual performance and firmness/hardness of erections, as well as enabling an increase in penile gauge and length [19].

Conclusion

LiSWT is a therapeutic alternative, non-invasive and very promising; the evidence supporting the usefulness of this therapy in ED is growing and increasingly solid. The main characteristic of LiSWT is its ability to rehabilitate erectile function, being, therefore, considered the only therapeutic modality with curative intent. However, the mechanisms through which LiSWT exerts its effects are not yet fully understood. Currently, there are not enough studies that clearly and consistently show the benefit of LiSWT in ED, with many conflicting results. LiSWT has been shown to be effective and safe in the treatment of ED of vasculogenic etiology; the clinical improvement of erectile function, reported through several validated questionnaires, together with the improvement of penile hemodynamics, aimed at in some of the studies presented, support the unique properties and positive effects that LiSWT has on erectile function. The potential of LiSWT to amplify the partial response to iPDE5 has also been studied, with auspicious results. Regarding the usefulness of LiSWT in ED secondary to radical prostatectomy, preclinical studies support its use, however, the existing clinical data are scarce and do not appear to support the usefulness of this therapy in post-surgical penile rehabilitation. With the acquisition of new knowledge that allows a better explanation about the main cellular pathways influenced by LiSWT and with the development of new clinical trials, which allow an optimization of the treatment protocols and an adequate screening of the candidates, it is expected that this new therapy will begin, in the near future, to be widely used in the treatment of ED, particularly in the vasculogenic subtype, as an alternative or as an adjunct to treatments already available.

Botulinum toxin is a modality with immense potential. Its conjectured mechanism of action is plausible and takes into account the pathophysiology of erection. The fact that it is a product that is routinely applied to smooth muscle in other territories, with reports of efficacy and safety, offers some confidence in its use at the penile level. The duration of action of Botox®, which can reach up to 12 months, is undoubtedly the main advantage of this therapy. Botulinum toxin, especially if combined with other pro-erectile drugs, when inserted in the therapeutic arsenal of ED, can revolutionize the approach of this pathology. However, it needs more studies so that it is possible to individualize it to subgroups of patients who can benefit from it.

PRP is another emerging treatment for ED that, even without scientific evidence, is provided diffusely throughout the world. With regard to this therapy, there seem to be more questions than answers. In fact, there seems to be a

propensity to accelerate patients' access to this treatment, which, although it may have a potentially valid benefit in ED, is not properly explored. Thus, it becomes evident that more studies will be needed, so that the real usefulness of PRP is elucidated.

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