PERSPECTIVE

The use of combination regenerative therapies for erectile dysfunction: rationale and current status

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Erectile Dysfunction (ED) is defined as the inability to achieve and maintain an erection sufficient for sexual intercourse. Available treatments for ED provide only symptomatic relief, which is for the most part temporary. Regenerative therapies such as Low Intensity Shockwave, Platelet-Rich Plasma, and Stem Cell therapy can potentially provide a "cure" for ED by reversing the underlying pathology of ED rather than just treating the symptoms. Low Intensity Shockwave therapy is the most evidence based at this point and is thought to act by improving penile blood flow, repairing previous nerve damage, and activating stem cells. Stem Cell therapy takes advantage of the self-replicative potential of stem cells to create new corporal tissue, but also to recruit host cells and angiogenic factors to stimulate endogenous repair. Platelet-Rich Plasma therapy uses concentrated growth factors that already exist within the bloodstream to repair damaged nerves and increase penile blood flow. The use of combination restorative therapy may provide an additive or synergistic benefit greater than any one therapy alone because of its overlapping mechanisms of action on the penis but is a topic that remains to be studied.

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INTRODUCTION

Erectile dysfunction (ED) is defined as, "the inability to achieve or maintain an erection that is sufficient for satisfactory sexual performance" [1]. The introduction of oral medications, penile injections, vacuum pumps, and even penile prosthetics have allowed for the treatment of ED symptoms without reversing underlying pathophysiology [2]. Furthermore, as treatment is only symptomatic, the relief provided through these modalities is for the most part temporary. Regenerative therapies such as Low Intensity Shockwave (LiSWT) [3–5], Platelet-Rich Plasma (PRP) [6], and Stem Cell therapy (SCT) [7] can potentially reverse the underlying pathology of ED rather than just treating the symptoms. In this article, we discuss regenerative therapies for ED including the possibility of using them in combination.

LOW INTENSITY SHOCKWAVE THERAPY (LISWT)

Shockwave therapy was first introduced to the field of Urology back in the 1970's aimed as a treatment for kidney stones [8]. LiSWT has more recently been adapted for use in treatment for ED [3, 9]. It works by distributing shockwaves in a targeted, localized area of the penile shaft (Supplementary Video). The resulting trauma and stress to the tissue promotes neovascularization, improves progenitor cell activation, and overall increases blood flow to the penis [3, 5, 10]. The efficacy for this treatment as a regenerative therapy has been the subject of multiple randomized controlled trials. A systematic review and meta-analysis performed by Clavijo et al. [11] analyzed seven trials to determine the effect of LiSWT on patients suffering from ED by assessing the change in International Index of Erectile Function – erectile function sub-domain (IIEF-EF) scores [12]. There was determined to be a clinically significant improvement in the IIEF-EF scores in those participants who underwent LiSWT (6.40 points) when compared with those who underwent a sham control treatment (1.65 points) [11]. Another systematic review by Feng et al. [13] analyzing patients who suffered from ED after radical prostatectomy examined multiple randomized controlled trials (RCT)s, one by Frey et al. [14], which observed an increase in IIEF-EF score (3.5 points) for patients treated by LiSWT, and another by Baccaglini et al. [15], which showed significantly increased IIEF-EF scores at 4 months for those patients treated by LiSWT.

There are, however, trials that have demonstrated no clinical significance of LiSWT for the treatment of ED including the ones by Yee et al. [16] and Fojecki et al. [17]. In both studies, there was no statistically significant results between their control and treatment groups when administered LiSWT.

The European Society of Sexual Medicine discussed the potential use of LiSWT in men with the vasculogenic subtype of ED with improvements seen up to 12 months post-treatment [4]. However, they refrain from providing a clear clinical recommendation due to the need for higher quality studies that enroll more patients and follow-up over a greater period of time to assess for the long term effects of LiSWT. The positions taken by the American Urological Association (AUA) and Sexual Medicine Society of North America (SMSNA) are similarly conservative, both considering LiSWT as still investigation that should be performed under strict Institutional Review Board (IRB) approved studies [18–20].

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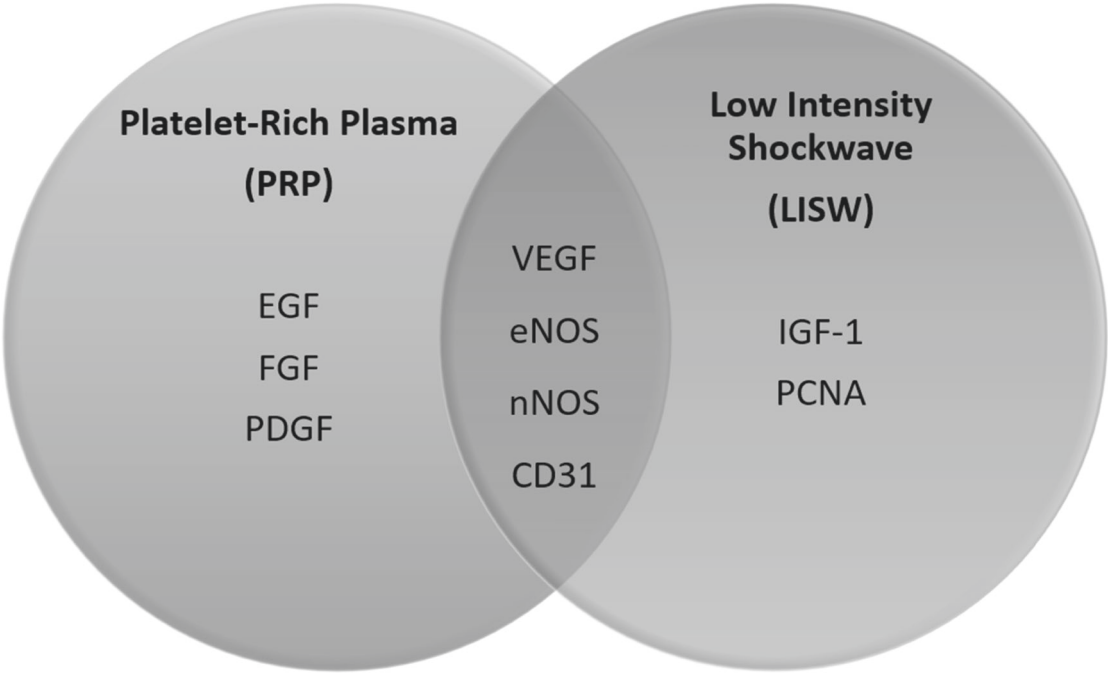

Abbreviations: EGF = epidermal growth factor; FGF = fibroblast growth factor; PDGF = platelet derived growth factor; VEGF = vascular endothelial growth factor; eNOS = endothelial nitric oxide synthase; nNOS = neuronal nitric oxide synthase; CD31 = Cluster of differentiation 31; IGF-1 = insulin like growth factor; PCNA = proliferating cell nuclear antigen

Fig. 1 Upregulated pathways involved with individual and combination therapy.

PLATELET RICH PLASMA (PRP)

PRP is autologous blood plasma with platelet concentrations that are 3–7 times greater than typical plasma and several growth factors. It has been described as a treatment in multiple specialties including orthopaedics [21], dermatology [22], and cardiothoracic surgery [23]. Recently studies have started to investigate the use of PRP for ED (Supplementary Video). Several growth factors are released from the platelets when activated after injection [24], and the most commonly studied are vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), and fibroblast growth factor (FGF). These growth factors have been shown to improve erectile function in preclinical models as well as early clinical studies [25–28]. VEGF mediated improvement in erectile function has been shown to work through the endothelial nitric oxide synthase (eNOS) pathway, and PRP has also been shown to facilitate nerve repair and regeneration in animal models [25, 26].

Clinical studies examining PRP in ED are still in their early stages. Matz et al. [27] conducted the first study in the United States to assess safety and feasibility of PRP injections for ED, Peyronie's disease (PD), and stress urinary incontinence (SUI). They administered intracavernosal PRP injections to 17 patients with ED, observed them in clinic for 20-30 min for complications, and administered International Index of Erectile Function (IIEF-5) questionnaires before and after treatment. This study found that the treatment was well tolerated and did not lead to any decline in IIEF-5. A systematic review conducted by Epifanova et. Al. [29] analyzed four preclinical studies and six clinical trials investigating PRP for male sexual dysfunction. Across the studies, PRP treatment showed little adverse effects. However, the studies conducted have all had small sample sizes or lacked control groups, therefore, further investigation is needed to determine true safety and effectiveness.

Currently, Ramasamy et al. at University of Miami are conducting a study investigating the role of PRP in ED with an estimated enrollment of 80 participants and a placebo group. This study's design and size address some of the flaws in the previous studies and is estimated to be complete in September of 2022 [30].

STEM CELL THERAPY (SCT) & STROMAL VASCULAR FRACTION THERAPY (SVF)

SCT involves isolation of Mesenchymal Stem Cells (MSCs) or Stromal Vascular Fraction (SVF), which is injected into penile tissue to stimulate endogenous repair. MSCs are a unique population of adult stem cells which can be found scarcely throughout the body, and in higher concentration in bone marrow, umbilical cord, and adipose tissue, among others [31]. MSCs have potential for significant clinical benefit in ED through improving endothelial function [32]; improving blood flow to the penis [33, 34], or from local implantation of cells into corporal tissue, and reversal of damage via paracrine effects [35, 36].

SVF is comprised of a mixture of adipose-derived stem cells, endothelial precursor cells, and immunomodulatory cells which are obtained from abdominal fat tissue [37]. SVF can be given as an injection into the penile tissue to restore erectile function (Supplementary Video), however, the evidence to support its use as a clinical therapy is scarce compared to other regenerative therapy options.

Human research in this field has explored a wide range of modalities and delivery techniques [38–41]. Although SCT has been studied and reported in multiple clinical and pre-clinical trials, currently there is no consensus on the optimal dose or delivery route of SCT to enact meaningful changes in erectile function.

COMBINATION REGENERATIVE THERAPY

The idea of using two or more regenerative therapies to treat ED in the same patient is novel—only preliminary data has been presented at academic conferences to the urologic community. Despite there being a paucity of data on the subject, this approach

merits discussion; if one were to "attack" ED with multiple therapies that each target different pathophysiological lead points, the sum benefit should be greater than that of each individual part. This might be especially relevant for men with a mixed subtype of ED that is challenging for the practitioner to treat and refractory to traditional monotherapy.

Ruffo et al. found the addition of PRP injections to weekly LiSWT sessions to improve several subjective measures of ED greater than with LiSWT sessions alone [42]. Similarly, improvements in penile hemodynamic parameters such as peak systolic velocity of the cavernosal artery [43] and associated resistance indices [29] have also been reported. A major postulated mechanism behind the regenerative properties of LiSWT is its ability to restore endothelial cell signaling and promote neoangiogenesis in the corpus cavernosa [5]. Moreover, almost all RCTs measuring the use of LiSWT for ED have been conducted on patients that have the vasculogenic subtype. PRP therapy however utilizes autologous growth factors, which may repair damaged endothelial cells and augment the development of new blood vessels initiated by LiSWT. The fact that the addition of PRP injections to LiSWT in the above studies led to better hemodynamic parameters in the penis is promising evidence of synergism that may be occurring when both therapies are combined (Fig. 1).

To date, the use of combination regenerative therapies for treating ED among human subjects has been limited to LiSWT + PRP. Only a few preclinical studies have examined the use of LiSWT with Stem cell or SVF [44], and data on other combinations of regenerative therapies is largely absent. Due to the high prevalence and quality of life burden that ED places on patients, utilizing a combination of regenerative therapies should be a focus of research moving forward for Men's Health specialists.

A WORD OF CAUTION

While regenerative ED therapies are exciting due to their potential for providing a "cure" for ED, there is not enough data to support their use in clinical practice. With the exception of LiSWT, very few RCTs exist that can attest to the efficacy of PRP, SCT, and SVF for treating ED. Similarly, while using a combination of regenerative therapies has hypothetical promise for treating moderate to severe ED, it is topic that is barely discussed in the literature, and more efforts are needed to promote this area of research in men's health. Robust clinical trials are needed to discern if individual, as well as combination has treatment efficacy compared to placebo. All forms of regenerative ED therapy that are offered should be disclosed as investigational only, and any treatment provided through these avenues should be in the context of IRB approved studies.

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COMPETING INTERESTS

RR is a consultant for Acerus Pharmaceuticals, Boston Scientific, Coloplast, Endo Pharmaceuticals, Metuchen, and Nestle Health. All other authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

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