The University of Miami, Miller School of Medicine
Desai Sethi Urology Institute

Clinical Research Protocol

Title:	**COMBINING SHOCKWAVE THERAPY AND PLATELET RICH PLASMA FOR TREATING ERECTILE DYSFUNCTION IN DIABETIC MEN (COCKTAIL-DM)**
Protocol No:	**UM IRB#: 20220540** **NCT#: NCT05525572**
Protocol Version:	**Version 1.3** **Version Date: 5/26/2023**

PI/Sponsor:	**Thomas A Masterson III, MD**
Telephone:	**(305) 243 – 6260** ***(24 hour)***
Fax:	**(305) 243 – 3381**
Email:	**TMasterson@med.miami.edu**

Investigator Signature Page

Title: **COMBINING SHOCKWAVE THERAPY AND PLATELET RICH PLASMA FOR TREATING ERECTILE DYSFUNCTION IN DIABETIC MEN (COCKTAIL-DM)**

I have read the enclosed protocol. I will ensure the safety of the study subjects enrolled under my supervision, and will provide the sponsor with complete, accurate, and timely information on this study, as outlined in this Protocol. The signature below constitutes approval of this protocol and the attachments and provides the required assurances that this trial will be conducted according to all stipulations of the protocol, including local legal and regulatory requirements, applicable US federal regulations and (ICF E6) guidelines. I shall hold strictly confidential all information pertaining to the study, and that this confidentiality requirement applies to all study staff at the site(s) and/or under my supervision.

Thomas A Masterson III, MD
Principal Investigator

5/26/23
Date

Principal Investigator Signature

Table of Contents

List of Abbreviations and Definition of Terms 5
Protocol Synopsis 6
Protocol Title 8
1. Background 8
1.1 Platelet-based therapies 8
1.2 Platelet-rich plasma treatment for erectile dysfunction 9
1.3 Energy-based treatments for erectile dysfunction 10
1.4 Combination Restorative Therapy for Erectile Dysfunction 10
2. Study Objectives 11
2.1 Primary Objective: 11
2.2 Secondary Objective: 11
3. Study Endpoints 11
3.1 Primary Endpoints 11
3.2 Secondary Endpoints (efficacy): 11
3.3 Exploratory Endpoints: 11
4. Study Location 11
4.1 Additional Study Sites 12
5. Study Population 12
5.1 Inclusion criteria: 12
5.2 Exclusion criteria: 12
6. Identification and Enrollment of Subjects 13
6.1 Recruitment and Pre-screening 13
6.2 Payment to Subjects 13
6.3 Informed Consent 13
6.4 Withdrawal Criteria 14
7. Procedures Involved 14
7.1 Schedule of Events: 14
7.2 Description of Study Procedures 16
7.3 Description of Study Visits 17
8. Investigational Product 18
8.1 Preparation of PRP 18
8.2 Administration of Investigational Therapies 18
9. Data Management 19
9.1 Case Report Forms (CRFs) 19
9.2 Source Documents 19
9.3 Study Monitoring, Auditing, and Inspecting 19
10. Data and Specimen Banking 20
10.1 Storage of Data 20
10.2 Specimen Banking 20
11. Safety Monitoring and Reporting 20
11.1 Adverse Events (AEs) 20
11.2 Serious Adverse Events (SAEs) 21
11.3 Treatment Emergent Serious Adverse Events (TE-SAEs) 21

12.7 Confidentiality and Objectivity 25
13. Statistical Considerations 25
13.1 Data Analysis Plan 25
14. Risks and Benefits 25
14.1 Risks to Subjects 25
14.2 Potential Benefits to Subjects 25
15. Privacy & Confidentiality 25
15.1 Data collection 26
15.2 Data Storage 26
15.3 Biospecimens 26
16. Ethical Considerations 26
16.1 Regulatory Authority Approval 26
16.2 Ethics Approval 27
16.3 Conflict of Interest 27
17. Publications 27
18. References 28

List of Abbreviations and Definition of Terms

AE	Adverse Events
BPH	Benign Prostatic Hyperplasia
BRB	Biomedical Research Building
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
ED	Erectile Dysfunction
EDITS	Erectile Dysfunction Inventory of Treatment Satisfaction
EDV	End Diastolic Velocity
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICI	Intracavernosal Injection
IEC	Institutional Ethics Committee
IIEF	International Index of Erectile Function
IIEF-EF	Erectile Function Subdomain Score
IRB	Institutional Review Board
ISCI	Interdisciplinary Stem Cell Institute
MCID	Minimal Clinically Important Difference
mL	Milliliter
ng/dL	Nanograms Per Deciliter
PDE5i	Phosphodiesterase 5 inhibitor
PPP	Platelet Poor Plasma
PRFM	Platelet Rich Fibrin Matrix
PRP	Platelet Rich Plasma
PSV	Peak Systolic Velocity
RCT	Randomized Controlled Trial
SAE	Serious Adverse Events
SEP3	Sexual Encounter Profile
SOP	Standard Operating Procedure
SWT	Low-intensity Shockwave Therapy
TE-SAE	Treatment Emergent Serious Adverse Events
UM	University of Miami
VAS	Visual Analogue Pain Scale

Protocol Synopsis	
TITLE	COMBINING SHOCKWAVE THERAPY AND PLATELET RICH PLASMA FOR TREATING ERECTILE DYSFUNCTION IN DIABETIC MEN (COCKTAIL-DM)
SPONSOR	University of Miami, Miller School of Medicine - Department of Urology
PHASE OF STUDY	Phase I/II
STUDY THERAPY	Autologous Platelet-Rich Plasma (PRP) + Low-intensity Shockwave Therapy (SWT)
STUDY DESIGN	Single arm, Open Label, Pilot Trial
ROUTE OF ADMINISTRATION	Intracavernosal Injection (PRP) + extracorporeal shockwave therapy (SWT)
SUBJECT POPULATION	15 male subjects between the age of 30-80 with Mild or Mild-to-Moderate ED and controlled Diabetes Mellitus (DM)
STUDY OBJECTIVES	Primary: To investigate biochemical markers of neo-angiogenesis in patients before and after PRP injection + SWT Secondary: To study efficacy and incidence of adverse events and safety of PRP injection + SWT treatment in men with mild-moderate ED, as measured by IIEF.
INVESTIGATION PLAN	15 men with Erectile Dysfunction (ED) of organic origin and Diabetes (Type 1 or Type 2), that meet all of the inclusion and none of the exclusion criteria, will be enrolled and will receive PRP+SWT. Autologous PRP injection + SWT therapy. All subjects in this group will receive 2 sessions of autologous PRP penile injection with 30 ± 7 day treatment interval. 5mL of PRP will be injected at each session. Additionally, patients will receive a total of 3600 shocks over a five-week period, starting at initial PRP injection.
DURATION OF STUDY	7 months (1 month screening, 5 weeks of therapy sessions, 6 months of follow-up).
DEFINITION OF ENDPOINTS	Primary: - Changes in markers of vasodilation (eNOS, nNOS), neo-angiogenesis (VEGF, CD-31), and systemic markers of endothelial function (EPCs, SDF-1α, and SCF). Secondary: - Differences in Doppler ultrasound parameters (PSV and EDV) from baseline to 6 months post-therapy. - Treatment satisfaction as assessed by EDITS questionnaire in all subjects. - Incidence of Serious Adverse Events experienced up to 6 months post-therapy. Exploratory: - Change in IIEF-EF score from baseline to 3 and 6 months post-therapy. - Percentage of subjects that achieve minimal clinically important difference (MCID) in IIEF-EF from baseline to 3 and 6 months post-therapy. Percentage of subjects who either decrease or discontinue use of PDE5i after three months post-therapy

Protocol Synopsis	
INCLUSION CRITERIA	1. Be Male 2. Be 30 to 80 years of age (inclusive). 3. Be able to provide written informed consent. 4. Have a diagnosis of mild to moderate ED (12-21) or mild ED (22-25) based on IIEF-EF questionnaire score. 5. Have diagnosis of Diabetes Mellitus (Type 1 or Type 2), as documented by history of Hemoglobin A1C > 7% OR on medical therapy for Diabetes. 6. Be in a stable relationship and have a minimum of 2 sexual attempts per month for at least one month prior to enrollment. 7. Agree to comply with all study related tests/procedures.
EXCLUSION CRITERIA	1. Previous penile surgery of any kind (except circumcision and condyloma removal), such as penile lengthening, penile cancer surgery, penile plication, grafting. 2. Previous history of priapism, penile fracture, Peyronie's Disease, or penile curvature that negatively influences sexual activity, 3. Abnormal morning serum testosterone level defined as a value lower than 300 ng/dL (±5%). 4. Psychogenic ED as determined by study investigator. 5. Patients using ICI for management of ED 6. Patients with generalized polyneuropathy, neurological conditions, or psychiatric disease (such as bipolar disorder or depression). 7. Have a serious comorbid illness or condition that, in the opinion of the investigator, may compromise the safety or compliance of the subject or preclude successful completion of the study. 8. History of consistent treatment failure with PDE5 inhibitors for therapy of ED. 9. Poorly controlled diabetes as indicated by Hemoglobin a1c > 7.5%. 10. Use of antiplatelet medication

Protocol Title

COMBINING SHOCKWAVE THERAPY AND PLATELET RICH PLASMA FOR TREATING ERECTILE DYSFUNCTION IN DIABETIC MEN (COCKTAIL-DM)

1. Background

1.1 Platelet-based therapies

Platelet-derived therapies are a growing trend across multiple medical and surgical specialties including dermatology, ophthalmology, cardiology, colorectal surgery, plastic surgery and mainly orthopedics [1-2]. One of the most well described platelet-based therapies is autologous platelet-rich plasma (PRP) [3]. PRP is derived from the centrifugation of whole blood with a separator gel to remove the red and white blood cells. The resulting supernatant has a greater than four-fold increase in platelets and other plasma proteins [1]. This concentrate is then administered via injection. PRP has been frequently used for orthopedic conditions such as bone and soft tissue trauma, inflammatory conditions, and chronic pain syndromes [3-4]. Evidence suggests that platelets play an important role not only in coagulation but also in regulation of body metabolism, promotion of the wound healing, tissue regeneration, vascular remodeling and inflammatory/immune responses through secretion of growth factors, cytokines and chemokines [4-5]. These biologically active proteins include transforming growth factor-β, platelet-derived growth factor, platelet-derived epithelial growth factor, insulin- like growth factor, vascular endothelial growth factor, basic fibroblast growth factor, as well as many others [6]. When platelets are activated, they release these growth differentiation factors, facilitating even nerve repair and regeneration [7-8]. Growth factors act locally and are implicated in many aspects of natural wound healing, including chemotaxis, cell proliferation, cell differentiation and angiogenesis. They also control and conduct synthesis, modification and degeneration of extracellular matrix proteins. Coordination of these cellular and molecular processes is integral to proper wound healing and tissue regeneration [9]. The key role of platelets in these processes makes them an attractive candidate for therapies aimed at accelerating natural healing, as well as tissue regeneration.

Autologous blood-based biomaterials are promising therapeutic options for varied pathology. Rapid generation of therapeutic material following collection allows for point-of- care therapy [10]. Furthermore, anautologous therapy avoids the need for immunosuppression and eliminates concerns of rejection. Newer strategies to prolong the anti-inflammatory and wound healing properties of platelets have focused on creating a fibrin matrix (platelet rich fibrin matrix, PRFM) to bind the platelets and prevent extravasation from the site of injection, thereby addressing the concern of early washout with PRP [11]. In addition, PRFM offers a potential scaffold for tissue ingrowth and may allow continued release of platelet-related factors for a longer duration. Across multiple disciplines, PRP has been used both as a primary treatment modality and as a supplement to other therapies in hopes of supplementing wound healing, tissue regeneration, and angiogenesis. Although most of the studies focusing on PRP injections have been relatively small and heterogenous, they largely support the concept of administration in terms of safety, while efficacy remains uncertain. Finally, the concept of

autologous therapy has be shown in the real world that it is particularly attractive to patients [10].

1.2 Platelet-rich plasma treatment for erectile dysfunction

Erectile dysfunction (ED) affects as many as 1 in 4 men, and evidence indicates that incidence is rising [12-13]. The pathophysiology is multifactorial, but the most common pathophysiology, vasculogenic erectile dysfunction, has as first sign endothelial dysfunction secondary to inflammation [14]. The most common treatments for ED aim to improve endothelial function through augmentation of the nitric oxide pathway [15]. Return of potency after surgical injury of CNS partially depends on axon regeneration in the remaining neural tissue [16]. The process of regeneration and functional recovery of peripheral nerve is slow and is influenced by many factors [17] such as extracellular matrix, neurotrophic factors, and cellular components [18]. Recent advances in the understanding of molecular pathways and their physiological role demonstrate that growth factors are an important part of the development, maintenance, and regeneration of the nervous system [19]. Various growth factor neuromodulatory strategies, including insulin-like growth factor (IGF-I) and neurotrophic factors, are investigated to identify agents that may have neuroprotective and regenerative function after the occurrence of peripheral nerve injury. Accumulating evidence indicates that neuroimmunophilin ligand (such as FK506) plays a significant role in neural regeneration and upregulation of neuronal nitric oxide synthase (nNOS), as well as in the recovery of erectile function after CN injury occurrence [20-21]. FK506 neuroprotection after CN injury is mediated by antioxidative/nitrosative and anti- apoptotic pathway [22]. When platelets are activated, they release many kinds of growth differentiation factors and a few types have been found to facilitate nerve repair and regeneration. Moreover, corporeal dysfunction due to smooth muscle atrophy or other inracavernosal pathology can lead to corporo-venous occlusive erectile dysfunction despite a normal arterial inflow. Rejuvenating the Corporeal tissues with PRP, which is well known for its growth and healing factors, is a possible modality as a potential treatment for erectile dysfunction according to Alkhayal et al [23]. In their retrospective study examining the efficacy of one intra-cavernosal PRP injection to 40 ED patients, they reported that mean IIEF-5 score before treatment was 13 (5-20) and post treatment IIEF-5 = 17 (7-24), ($p < 0.001$). Other studies have shown similar results with minimal side effects, no serious adverse reactions and potential efficacy (Table 1) [23-26].

Human Studies of PRP for ED							
Author	**Year**	**Number of Patients**	**Patient Population**	**Administration**	**Followup**	**Adverse Events**	**Conclusion**
Banno [26]	2017	N=9	Penile Rehab	PRP ICI into Pnies with Vacuum Device	4 weeks	No AEs reported	PRP may represent a safe and viable option as a supplementary therapy for penile rehabilitation. Particularly notable is the prospect of zero side effects.
Matz [24]	2018	N=16	Erectile dysfunction, Peyronies Disease	PRP with CaCl ICI	15.5m	Minor: Bruising 1, Mild Pain 4. Major: none	PRFM injections for ED, PD, and female SUI are feasible and safe. Although the limited data is suggestive of efficacy, a placebo control will be required in subsequent efforts for confirmation
Epifanova [25]	2019	N=10	Erectile Dysfunction	6 injections PRP with CaCl2 ans Shockwave	60 Days	No AEs reported	There were no serious adverse events as well as severe adverse events. Erectile dysfunction symptoms in all men participated in the study significantly decreased after treatment with PRP-therapy and extracorporeal shockwave therapy
Alkhayal [23]	2018	N=40	Erectile Dysfunction	1 injection PRP	> 1 month	No AEs reported	Platelet rich plasma is a safe and efficacious option for penile rejuvination and improvement of erectle dysfunction

Table 1: Summary of published studies and abstracts

To date, there are no treatments that address the underlying cause of endothelial dysfunction, although LIST treatment for ED has shown promising results. Platelet-derived therapies targeting inflammation and promoting tissue/nerve regeneration and may represent a potential treatment option towards this direction. Despite growing evidence to the efficacy of PRP, no randomized placebo-controlled studies exist.

1.3 Energy-based treatments for erectile dysfunction

Shockwave therapy has been utilized by urologists for other ailments, such as treatment of kidney stones through a non-invasive manner. Interest in the use of low-intensity shockwave therapy for erectile dysfunction was augmented with success seen in preclinical models. The hypothesis for SWT's mechanistic actions is neo-angiogenesis, recruitment of progenitor cells and resident stem cells, improvement of microcirculation, vasodilation with subsequent increase in nitric oxide, decrease in fibrosis, and nerve regeneration. There have been 13 published clinical studies regarding use of SWT for ED. Multiple systematic reviews and meta-analyses have been performed for SWT for ED, and there is consensus that SWT shows promise in the treatment for ED.

1.4 Combination Restorative Therapy for Erectile Dysfunction

The development of ED therapeutics that focus on neurovascular regeneration and repair strategies are of great importance. A large body of *pre-clinical* work has demonstrated the effect of SWT alone (monotherapy) on angiogenesis and progenitor / stem cell recruitment for ED [2, 3, 8-11]. PRP monotherapy importantly is also supported by well-defined mechanistic insights obtained from rigorously conducted animal studies [12-19]. All the previous studies in humans have evaluated either IIEF scores and / or penile Doppler ultrasound hemodynamic parameters, but there has not been evaluation of the treatment as a combination. The proposed mechanisms of both interventions would

suggest that the combination therapy would act in a synergistic manner, with superiority over monotherapy. Success of our proposed work could fundamentally change the standard of care for ED and substantially improve the quality of life for tens of millions of men.

2. Study Objectives

2.1 Primary Objective:

To investigate of the underlying mechanisms of PRP and SWT in men with mild-moderate ED and Diabetes.

Exploratory:

- Change in IIEF-EF score from baseline to 3 and 6 months post-therapy.
- Percentage of subjects that achieve minimal clinically important difference (MCID) in IIEF-EF from baseline to 3 and 6 months post-therapy.
- Percentage of subjects who either decrease or discontinue use of PDE5i after three months post-therapy

2.2 Secondary Objective:

To study the treatment safety and efficacy of PRP and SWT treatment in men with mild-moderate ED and Diabetes.

3. Study Endpoints

3.1 Primary Endpoints

- Changes in markers of vasodilation (eNOS, nNOS), neo-angiogenesis (VEGF, CD-31), and systemic markers of endothelial function (EPCs, SDF-1α, and SCF).

3.2 Secondary Endpoints (efficacy):

- Differences in Doppler ultrasound parameters (PSV and EDV) from baseline to 6 months post-therapy.
- Treatment satisfaction as assessed by EDITS questionnaire in all subjects.
- Incidence of Serious Adverse Events experienced up to 6 months post-therapy.

3.3 Exploratory Endpoints:

- Change in IIEF-EF score from baseline to 3 and 6 months post-therapy.
- Percentage of subjects that achieve minimal clinically important difference (MCID) in IIEF-EF from baseline to 3 and 6 months post-therapy.
- Percentage of subjects who either decrease or discontinue use of PDE5i after three months post-therapy

4. Study Location

The study will be funded by the CTSI pilot award (GR019191) and coordinated by the University of Miami (UM), Miller School of Medicine, Desai Sethi Urology Institute. All

study visits will take place in the Department of Urology clinics, (PAC: 1150 NW 14th Street, Suite 309, University of Miami Miller School of medicine, Miami, FL. & Lennar: 5555 Ponce De Leon, 3rd floor, Coral Gables, FL.) PRP preparation and SWT therapy administration will take place in the PAC andrology lab and clinic.

4.1 Additional Study Sites

No additional study sites.

5. Study Population

15 males with ED of organic origin and diabetes. All patients will be regular PDE5i users/responders. Men with ED will be evaluated by IIEF-EF domain and eligible patients will be enrolled in this open label pilot study. Participants who do not meet eligibility criteria will be considered a screen failure and will not receive the study therapy.

5.1 Inclusion criteria:

In order to participate in this study, a patient must:

1) Be Male.
2) Be 30 to 80 years of age (inclusive).
3) Be able to provide written informed consent.
4) Have a diagnosis of mild to moderate ED (12-21) or mild ED (22-25) based on IIEF-EF questionnaire score.
5) Have diagnosis of Diabetes Mellitus (Type 1 or Type 2) as documented by history of hemoglobin A1C > 7% OR on medical therapy for Diabetes.
6) Be in a stable relationship and have a minimum of 2 sexual attempts per month for at least one month prior to enrollment.
7) Agree to comply with all study related tests/procedures.

5.2 Exclusion criteria:

In order to participate in this study, a patient must not have any of the following:

1) Previous penile surgery of any kind (except circumcision and condyloma removal), such as penile lengthening, penile cancer surgery, penile plication, grafting.
2) Previous history of priapism, penile fracture, Peyronie's Disease, or penile curvature that negatively influences sexual activity.
3) Abnormal morning serum testosterone level defined as a value lower than 300 ng/dL (±5%).
4) Psychogenic ED as determined by study investigator.
5) Patients using ICI for management of ED
6) Patients with generalized polyneuropathy, neurological conditions, or psychiatric disease (such as bipolar disorder or depression).
7) Have a serious comorbid illness or condition that, in the opinion of the investigator, may compromise the safety or compliance of the subject or preclude successful completion of the study.
8) History of consistent treatment failure with PDE5 inhibitors for therapy of ED.
9) Poorly controlled diabetes as indicated by Hemoglobin a1c > 7.5%.
10) Use of antiplatelet medication.

6. Identification and Enrollment of Subjects

6.1 Recruitment and Pre-screening

The research coordination team may develop materials to aide in recruitment. This may include, but is not limited to, informational videos and brochures which provide education about erectile dysfunction and include information about the study; physician referral letter templates which can be used to promote awareness of the study in the urology community; flyers/posters which can be utilized at approved clinic locations and as part of health fair materials; templates for print advertisements which can be utilized in newsprint and media campaigns. Not all materials have been developed prior to trial initiation, however each of these recruitment methods will be reviewed and approved by the IRB prior to use.

Pre-screening of subjects includes reviewing medical records and imaging studies for inclusion/exclusions prior to consent. From the review of subjects' medical records and imaging studies on file, subjects who are determined to have a diagnosis of erectile dysfunction of organic origin and have mild-moderate erectile function as assessed by IIEF-EF, as stated in Section 5.1, and also do not have evidence in their medical record of study exclusions stated in Section 5.2, are eligible to be consented to the study.

Investigators will inform research staff of potential participants who have been identified through pre-screening so the subjects can be approached to discuss the study and conduct the informed consent session. No study procedures will take place prior to the subjects signing of the informed consent form.

6.1.1 Waiver of Authorization for Use and Disclosure of Protected Health Information (HIPAA)

A partial waiver of HIPAA is requested for recruitment purposes only. All Protected Health Information (PHI) collected by the study investigator and/or study personnel from patient records JHS and/or UHealth will be destroyed at the earliest opportunity. All Protected Health Inform (PHI) that is acquired from JHS and/or UHealth will not be re-used or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

6.2 Payment to Subjects

No payments will be made to subjects as compensation for their participation in this study. The subjects will not be asked to pay for the treatments or participation in study either.

6.3 Informed Consent

6.3.1 Consenting Process

All subjects must provide written consent to participate in this study. An informed consent form (ICF) will be given to each subject. The ICF will contain all United States federally required elements, all International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) required elements, and Health Insurance Portability and Accountability Act Authorization (HIPAA) information in language that is understandable to the subject. The informed consent includes descriptions of all study related procedures, all possible risks to participant, and

the time commitment involved with participating. All consent forms will have IRB approval. The ICF must be understandable to the subject. Translation of ICFs will be done in accordance with local IRB procedures.

Potential participants will be approached by one of the study investigators or research coordinators. Information regarding study participation will be provided to the potential participant prior to consent. Subjects will be given ample time to review the ICF and ask questions before signing. The Investigator or designee and the subject must both sign and date the ICF after review, and before the any study procedures are performed. The subject will receive a copy of the signed and dated form, and the original will be retained in the site study files. The research staff member obtaining consent will document the informed process in the subject's chart for monitoring purposes. The Investigator or his/her designee must emphasize to the subject that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

6.3.2 Non-English-Speaking Subjects

In addition to English-speaking subjects, Spanish-speakers will also be included in the trial. A certified translated version of the IRB approved English consent form will be made available to non-English speakers. Spanish version questionnaires and other patient-facing materials will also be made available.

6.4 Withdrawal Criteria

All subjects who either screen fails, is withdrawn from the study, or has completed all visits should be de-enrolled from the research database within 2 business days, in accordance with university policies (or respective institutional policy).

Subjects may be withdrawn from the study for any of the following reasons:

a) A subject does not meet the eligibility criteria (the subject will be considered a screen failure).

b) A subject withdraws consent.

c) A subject expires during protocol participation from causes other than the study treatment (not due to adverse events).

d) At the discretion of the principal investigator for issues of non-compliance, or other behavioral factors.

7. Procedures Involved

15 men with Erectile Dysfunction (ED) of organic origin, that meet all of the inclusion and none of the exclusion criteria, will be enrolled to receive PRP+SWT in an open-label fashion.

Autologous PRP injection + SWT therapy. All subjects in this group will receive 2 sessions of autologous PRP penile injection with 28 ± 2 day treatment interval. 5mL of PRP will be injected at each session. Additionally, patients will receive a total of 3600 shocks over a five-week period, starting at initial PRP injection.

7.1 Schedule of Events:

The events table for the conduct of this study is shown below:

Table1:

Schedule of Events		Screening	Treatment					Follow Up	
Time Point / Event		0-30 days before randomization	Week 0 Day 0	Week 1 Day 7 ± 2	Week 2 Day 14 ± 2	Week 3 Day 21 ± 2	Week 4 Day 28 ± 2	Month 3 Day 90 ± 14	Month 6 Day 180 ± 14
Informed Consent		X							
Demographics		X							
Medical History		X							
Physical Exam		X							
Doppler Ultrasound		X							X
Questionnaires	IIEF	X						X	X
	EDITS							X	X
	VAS		X	X	X	X	X		
Laboratory Tests*		X							
EPC-CFUs		X						X	X
Brachial FMD		X						X	X
PRP Injection			X				X		
Shockwave Therapy			X	X	X	X	X		
Concomitant Medications/Therapy		X	X	X	X	X	X	X	X
Review Adverse Events			X	X	X	X	X	X	X

7.2 Description of Study Procedures

7.2.1 ***Informed Consent:*** Refer to Section 6.3 for details regarding the informed consent process. Study procedures will be completed only after participants have signed the informed consent documentation.

7.2.2 ***Demographics:*** Demographic characteristics will be recorded including: date of birth, gender, marital status, race and ethnicity.

7.2.3 ***Medical History:*** Assessment of current and past medical, surgical, and social history will be conducted.

7.2.4 ***Physical Examination:*** Genitourinary/Reproductive system physical exam will be performed.

7.2.5 ***Doppler Ultrasound:*** Penile Doppler ultrasound will be performed as standard of care for the management of erectile dysfunction. Results from within the past 12 months can be extracted from the medical record for use in this study.

7.2.6 ***International Index of Erectile Function (IIEF) Questionnaire*****:** This validated 15-item self-evaluation scale provides pre and post treatment clinic evaluations of erectile function, orgasmic function, sexual desire, satisfaction in sexual intercourse and general satisfaction. If the subject has completed the IIEF questionnaire within the past 6 months, those results may be requested and used for the purpose of this research study. Questionnaires will be completed prior to therapy at injection visits.

7.2.7 ***Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) Questionnaire*****:** This is a psychometrically sound questionnaire used to assess satisfaction with medical treatment modalities for erectile dysfunction.

7.2.8 ***Visual Analogue Pain Scale (VAS)*****:** The visual analog scale (VAS) is a validated, subjective measure for acute and chronic pain. Scores are recorded by making a handwritten mark on a line that represents a continuum between “no pain” and “worst pain”.

7.2.9 ***Laboratory Testing:*** Hematology, chemistry, hemoglobin A1C, and serum testosterone lab test results will be collected at screening. If any standard of care labs testing has been performed within 12 months of the date of the screening visit, those results may be used for the purpose of this study.

7.2.10 ***Endothelial Progenitor Cell Colony Forming Units (EPC-CFUs):*** Peripheral blood samples will be collected from participants for isolation of EPCs using Ficoll-Paque density gradient. Plasma will be aliquoted and stored for future analysis. Five million cells will be seeded on 6-well Fibronectin-coated dishes (BD Biosciences) in CFU-Hill medium (Stem Cell Technologies, cat#05900)4 and incubated at 37^{o}C in humidified 5% CO2. Non-adherent cells will be collected after 48 hours, and 1 million cells will be seeded on 24-well Fibronectin-coated dishes. On day 5, EPC-CFUs will be counted in 6 wells and the average will be obtained.

7.2.11 ***Brachial Artery Flow Mediated Dilation (FMD):*** FMD% is a non-clinical measure; it is a tool used specifically for research to obtain an understanding the functionality of the vascular endothelium. 2D ultrasound will be used to measure Flow Mediated

Diameter percent change (FMD%). All measurements of the brachial artery diameter and FMD% will be performed in the morning, in a quiet and dark room and at controlled ambient temperature. Subjects will fast overnight and refrain from consuming caffeine, nicotine, or other stimulants for at least 8 hours prior to ultrasound and should refrain from vigorous exercise for at least 4 hours prior to ultrasound. Subjects are permitted to drink water and take medications (except PDE5 inhibitors) as usual. The subject will rest for 10 minutes in the supine position prior to scan. The subject's right arm will be comfortably immobilized in an extending position, allowing for ultrasound scanning of the brachial artery 5–10 cm above the antecubital fossa. In each examination, recording of vessel images will be followed by inflation of a cuff to supra-systolic pressure (40 to 50 mmHg above systolic pressure) for 5 minutes. Then the cuff will be deflated, and the brachial artery diameter will be imaged and recorded for 3 minutes.

7.2.12 ***Platelet-Rich Plasma (PRP) Injection*****:** Approximately 120mL of blood will be collected from participants for preparation of investigational product. Refer to Section 8 for description of Investigational Product (IP) preparation and administration.

7.2.13 ***Shockwave Therapy (SWT)*****:** In the treatment group, patients randomized will receive 5 weekly sessions, in which 720 shocks of treatment energy will be applied in every session to each treated region (left and right corpora cavernosa and crura) for a total of 3,600 shocks. Refer to Section 8 for description of Investigational Product (IP) preparation and administration.

7.2.14 ***Concomitant Medications:*** Review of current use of prescription and over the counter (OTC) medications. Participants must discontinue use of PDE5i medications throughout the duration of the study.

7.2.15 ***Review Adverse Events:*** Refer to Section 11 for description and reporting of adverse and serious adverse events

7.3 Description of Study Visits

7.3.1 Screening Visit

Visit 1 (0 – 28 days before therapy): The basic work-up will take place, including medical and sexual history, as well as necessary lab tests (testosterone, prolactin, hematology, chemistry), if not available during the last 12 months prior to screening. Subjects will complete the IIEF questionnaire. We will ensure that patients have 4 attempts for intercourse Screening visit can occur on same day as first injection + SWT. Refer to table 1 for procedures to be performed at the Screening visit.

7.3.2 Treatment Visits: Week 0 – Week 4

Upon evaluation of eligibility, subjects will be randomized to one of the two parallel study groups using an online program, and initiate treatment on the same day.

There will be 5 treatment visits for all groups, each occurring at weekly intervals (± 2 days), for a total duration of five weeks. Subjects will complete a Visual Analogue Scale (VAS) pain score after the end of each treatment. Refer to table 1 for all procedures to be performed at the treatment visits.

7.3.3 Follow Up Visits: Months 3 and 6 Post-Treatment

Follow up visits will occur within 90 ± 14 days (Month 3) and 180 ± 14 days (Month 6) days after final treatment visit. Refer to table 1 for procedures to be performed at the follow up visits visit.

8. Investigational Product

8.1 Preparation of PRP

Autologous Platelet-Rich Plasma (PRP) is prepared by taking 120 mL aliquots of anticoagulated peripheral blood (120 mL whole blood and 16 mL anticoagulant citrate dextrose formula A) obtained from each subject by venipuncture. Each aliquot is processed by an autologous platelet separator (Arthrex Angel, Arthrex Inc., Naples, Florida) to yield 3-10 mL of PRP from each subject. Platelet poor plasma (PPP) can be added to PRP to achieve the desired injection volume. This system is FDA approved by 510(k) for "clinical laboratory or intraoperatively at the point of care for the safe and rapid preparation of platelet poor plasma and platelet concentrate (platelet rich plasma) from a small sample of whole blood or a small mixture of blood and bone marrow". For participants randomized to the control arm, blood will still be drawn but will not be processed to make PRP.

8.2 Administration of Investigational Therapies

8.2.1 Platelet-Rich Plasma

The patient will be positioned supine. A sterile field will be developed with Betadine prep of the genitalia, sterile gloves and a sterile extremity drape. A total of 20 mL of 1% lidocaine will be drawn up using an 18-gauge needle and will be subcutaneously administered using a 27-gauge needle into the subcutaneous tissue at the base of the penis to obtain a dorsal nerve block. A 1/4-inch Penrose drain will be used as a tourniquet by placing it at the base of the penis and maintaining it in place under tension by a sterile clamp. A maximum of 5 mL of PRP will be infused steadily over a two-minute period – approximately 2.5 mL each into the right and left corpus cavernosum, as shown in Figure 1. The injections will be performed at this slow speed (each side over 2 minutes of infusion) to minimize injury to the platelet cells. In the control arm, men will be administered injectable normal saline that will be injected in a similar manner as the PRP.

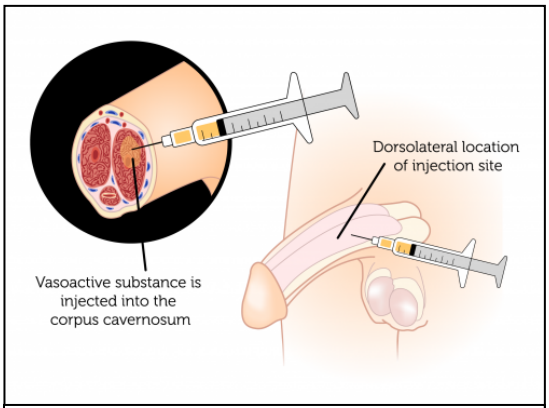

Figure 1: Diagram of PRP Injection

Following administration of PRP or normal saline, compression of the penis will be achieved with a clenched fist for 20 minutes. At 20 minutes, the tourniquet will be removed, and a compressive dressing will be placed around the penile shaft. The patient will be instructed to remove the compression bandage in 4 hours and to contact the study coordinators if he experiences any problems.

8.2.2 Low Intensity Shockwave Therapy

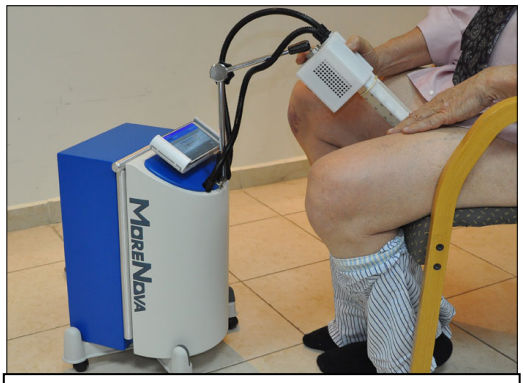

Figure 2: MoreNova SWT Device

Figure 2 shows the MoreNova device, which is a Linear Shockwave (LISW) transducer capable of delivering shockwaves to a treatment region confined to a narrow rectangle. Shockwaves generation follows the electromagnetic principle. Linear Shockwaves (LISW) has been under evaluation, as a treatment for ED for the last five years. The present study will utilize a device called "MoreNova", in which shockwaves are focused onto line segments for improved organ coverage. Shockwaves produced by "MoreNova" are aimed at the left and right corpora cavernosa and the crura. The study is aimed at determining the safety and efficacy of this new type of LISW in the treatment of ED. The treatment session lasts approximately 20 minutes and may be performed in an office environment. Treatment is applied in the physician's office.

All subjects will receive 5 weekly sessions, in which 720 shocks of treatment energy will be applied in every session to each treated region (left and right corpora cavernosa and crura).

9. Data Management

Data will be entered from source documents into eCRFs which are maintained in an online research database. The investigator will ensure data integrity by confirming the CRF's are attributable, legible, contemporaneous, original, accurate, and complete.

9.1 Case Report Forms (CRFs)

The Investigator or designee must record all required subject data, and an explanation must be documented for any missing data. This study will use electronic case report forms (eCRF) for data entry and database storage.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, and records kept at medical technical departments involved in the clinical trial. All corrections to study data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary, in accordance with good clinical practice (GCP) guidelines.

9.3 Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents. The investigator will ensure the capability for inspections of applicable study-related facilities.

10. Data and Specimen Banking

10.1 Storage of Data

Data will be maintained on research team hardware, and subject charts will be stored in a filing room maintained by Department of Urology. Clinical follow up and laboratory data will be stored in a locked room, with access only to authorized personnel. It is up to the principal investigator's discretion as to how long non-FDA study essential documents are retained.

10.2 Specimen Banking

Bio-specimens will be reserved for future testing and stored at -80 degrees Celsius in equipment maintained by ISCI in the Biomedical Research Building (BRB) (address: 1501 NW 10th avenue Miami FL 33136). Each specimen must have a corresponding requisition form to track the chain of custody from time of collection to time of processing and/or storage.

11. Safety Monitoring and Reporting

11.1 Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study. The event does not need to have a causal relationship with treatment. Common Terminology Criteria for Adverse Events Version 5 (CTCAE) will be used for describing AEs. All urological and/or reproductive system AEs will be recorded. For all other AEs, only events greater than grade 2 will be recorded.

Based on our own pilot data assessing SWT and PRP monotherapy, we have compiled the following data on adverse events (Table 2):

We anticipate there to be few adverse events related to the study. Based on the four published studies and abstracts, including 75 men, only minor adverse events were reported (Bruising 1, Mild Pain 4). No serious adverse events were observed [23-26].

SWT related adverse events	
Transient mild cutaneous purpura	0.10%
Local erythema	0.50%
Local swelling/edema	1.00%
Transient local anesthesia or paranesthesia	1.10%

PPR related adverse events	
Pain greater than 5/10 at time of injection	5.00%
Pain lasting > 5 days	5.00%
Penile bruising	0.00%
Penile fracture	0.00%

11.1.1 Expectedness

An adverse event is considered "unexpected" if it is not listed in the investigator brochure, protocol, ICF, or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

Anticipated adverse events for this study include: Pain, Bruising, Swelling, Edema, Allergy, Penile Fracture, and/or New Penile Curvature.

11.1.2 Severity

Common Terminology Criteria for Adverse Events, Version 5 (CTCAE v5.0) will be used to assess severity of adverse events. All grade 3-5 adverse events, regardless of association with the investigational therapy, will be entered into study database and reviewed at research committee meetings.

11.2 Serious Adverse Events (SAEs)

A serious adverse event (SAE) is defined as an AE which, in the view of the Investigator results in: 1) Death; 2) a life-threatening event (i.e. an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe); 3) inpatient hospitalization of > 24 hours or prolongation of existing hospitalization; 4) a significant disability/incapacity; or 5) a congenital anomaly/birth defect. Other important medical events may be considered SAEs if, in the opinion of the Investigator, they jeopardize the subject or require intervention to prevent one of the other outcomes listed above. Based on prior investigations, we do not anticipate any SAEs related to the study procedures [23-26].

11.3 Treatment Emergent Serious Adverse Events (TE-SAEs)

A treatment emergent serious adverse event (TE-SAE) is defined as any serious adverse event for which there is a reasonable possibility that the investigational product caused the adverse event. For the purposes of safety reporting, “a reasonable possibility” means there is evidence to suggest a causal relationship between the study product/procedures and the adverse event.

12. Statistical Considerations

12.1 Data Analysis Plan

Analysis plan: Continuous data will be analyzed using ANOVA with repeated measures, or student’s T-Test (where applicable) in order to compare differences between the treatment and control groups. For categorical data, Fisher’s Exact test to determine differences between groups. Statistical significance will be evaluated using $\alpha=0.05$.

13. Risks and Benefits

13.1 Risks to Subjects

We anticipate there to be few adverse events related to the study. Based on the four published studies and abstracts, including 75 men, only minor adverse events were reported (Bruising 1, Mild Pain 4). No serious adverse events were observed [23-26]. After literature review, we believe this product to be of non-significant risk to patients (NSR) and for investigational use in a clinical study protocol.

Based on published studies, we will record anticipated adverse events to patients include: local injection site reaction, penile pain, penile hematoma (bleeding into the tissue), penile swelling, allergic reaction to the anesthetic, local infection, penile fracture, or new penile curvature. In addition, there may be uncommon or previously unknown risks that might occur. We will record every adverse event at every visit systematically.

13.2 Potential Benefits to Subjects

The potential benefits for men randomized to the treatment arm will include improvement in erectile function and sexual performance.

14. Privacy & Confidentiality

Each subject's protected health information will remain strictly confidential and shall be excluded from the database. Patients deemed eligible to participate in the study following evaluation of inclusion/exclusion criteria will be assigned a unique study participant identifier number (ex.: COC-DM-01). The first two characters indicate the enrolling site, next 5 characters describe the study and phase, and final 3 characters are the unique identification number assigned to subjects in sequential order.

The Investigator will retain a cross-referencing record of each subject's name and assigned identifier number. All study data and results will be stored in the electronic database. Each study subject will give explicit consent for representatives of the IRB/IEC and regulatory authorities to inspect and verify each subject's medical records and collected information. In turn, each study subject will be assured that all their personal information will be maintained in the strictest of confidence, and in compliance with HIPAA, and all other federal and local laws regulating privacy and data protection.

Data will be collected from the EMR or subjects at UHealth or JHS. Research subjects will sign a HIPAA Authorization before collection of data for this research study.

14.1 Data collection

Data will include Protected Health information or Personally Identifiable Information.

14.2 Data Storage

Information will be stored on a University of Miami electronic device (e.g. encrypted, password-protected computer), and on a cloud-based storage system that is approved by the University of Miami. Research data will be entered into the REDCap secure electronic database.

The Principal investigator (and/or Study Team members) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers of any subject. Instead, the Principal Investigator and/or Study Team members will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. The link to each subject's identity and/ or other identifiable information will be maintained on a document separate from the research data.

14.3 Biospecimens

Biospecimens obtained for this research will be stored in a de-identified, coded manner without any direct or indirect identifiers. Biospecimens obtained for this research will be stored. When required to transport data or biospecimens for this research, the research team will transport the data and biospecimens in a de-identified (or anonymous)manner with a link to the individual subject's identity maintained separately from the data and/or biospecimen.

15. Ethical Considerations

15.1 Regulatory Authority Approval

This study will be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on

Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines and all applicable regulations, including current United States Code of Federal Regulations (CFR), Title 21, Parts 50, 54, 56, and Title 45, Part 164. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. This study will also be carried out in accordance with local legal requirements.

According to FDA guidance issued to institutional review boards and investigators, we will use PRP for ED (an indication not approved on the labeling) while simultaneously "bearing the responsibility to be well informed about the product, base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects."

We believe that according to FDA regulation**,** the clinical investigation of PRP and SWT for ED does not require submission of an IND / IDE since all six of the following conditions are met:

i. it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

ii. it is not intended to support a significant change in the advertising for the product;

iii. it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

iv. it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];

v. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and

vi. it does not intend to invoke 21 CFR 50.24.

15.2 Ethics Approval

The investigators agree to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics.

It is the Investigator's responsibility to ensure that, prior to initiating this study, this protocol is reviewed and approved by the appropriate local and/or external IRB. The composition and conduct of this committee must conform to the United States CFR. The IRB/IEC must also review and approve the site's informed consent form (ICF), other written information provided to the subject.

If it is necessary to amend the protocol or the ICF during the study, the Sponsor-Investigator will be responsible for ensuring that the IRB/IEC reviews and approves these amended documents. An IRB/IEC approval of the amended protocol and/or ICF must be obtained in writing before implementation of the amended procedures and before new subjects are consented to participate in the study using the amended version of the ICF.

15.3 Conflict of Interest

Any investigator who has a conflict of interest with the study must have the conflict reviewed by a properly constituted Conflict of Interest Committee with the Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All investigators will follow the University of Miami's (or applicable institution's) conflict of interest policy.

16. Publications

The preparation and submission of manuscripts for publication that contain results from this study shall comply with all applicable privacy laws and in accordance with processes determined by the University of Miami, Miller School of Medicine.

17. References

1. Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. Nat Rev Rheumatol 2013;9:721-30.
2. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. Curr Rev Musculoskelet Med 2008;1:165-74.
3. Xie X, Zhang C, Tuan RS. Biology of platelet-rich plasma and its clinical application in cartilage repair. Arthritis Res Ther 2014;16:204.
4. Randelli P, Randelli F, Ragone V, Menon A, D'Ambrosi R, Cuc- chi D, et al. Regenerative medicine in rotator cuff injuries. Biomed Res Int 2014;2014:129515.
5. Galliera E, Corsi MM, Banfi G. Platelet rich plasma therapy: inflammatory molecules involved in tissue healing. J Biol Regul Homeost Agents 2012;26(2 Suppl 1):35S-42S.
6. Nurden AT, Nurden P, Sanchez M, Andia I, Anitua E. Platelets and wound healing. Front Biosci 2008;13:3532-48.
7. Lin G, Shindel AW, Fandel TM, Bella AJ, Lin CS, Lue TF. Neurotrophic effects of brain-derived neurotrophic factor and vascular endothelial growth factor in major pelvic ganglia of young and aged rats. BJU Int 2010;105:114–20.
8. Apel PJ, Ma J, Callahan M, Northam CN, Alton TB, Sonntag WE, Li Z. Effect of locally delivered IGF-1 on nerve regen- eration during aging: An experimental study in rats. Muscle Nerve 2010;41:335–41.
9. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev 2003;83:835-70.
10. Kushida S, Kakudo N, Morimoto N, Hara T, Ogawa T, Mitsui T, et al. Platelet and growth factor concentrations in activated platelet-rich plasma: a comparison of seven commercial sepa- ration systems. J Artif Organs 2014;17:186-92.
11. Gigante A, Del Torto M, Manzotti S, Cianforlini M, Busilac- chi A, Davidson PA, et al. Platelet rich fibrin matrix effects on skeletal muscle lesions: an experimental study. J Biol Regul Homeost Agents 2012;26:475-84
12. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Construction of a surrogate variable for impotence in the Massachusetts Male Aging Study. J Clin Epidemiol 1994;47:457-67.
13. Derby CA, Araujo AB, Johannes CB, Feldman HA, McKinlay JB. Measurement of erectile dysfunction in population-based studies: the use of a single question self-assessment in the Massachusetts Male Aging Study. Int J Impot Res 2000;12:197-204.
14. Vlachopoulos C, Aznaouridis K, Ioakeimidis N, Rokkas K, Vasiliadou C, Alexopoulos N, et al. Unfavourable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. Eur Heart J 2006;27:2640-8
15. Li J, Shi Q, Pu C, Tang Y, Bai Y, Yuan H, et al. Phosphodiester- ase type 5 inhibitors for the treatment of post-nerve sparing radical prostatectomy erectile dysfunction in men. Sci Rep 2014;4:5801.
16. Mulhall JP. Penile rehabilitation following radical prostatec- tomy. Curr Opin Urol 2008;18:613 20.
17. Ge XX, Spector GJ, Carr C. The pathophysiology of com- pression injuries of the peripheral facial nerve. Laryngoscope 1982;92:1–15.
18. Seckel BR. Enhancement of peripheral nerve regeneration. Muscle Nerve 1990;13:785–800.
19. Frostick SP, Yin Q, Kemp GJ. Schwann cells, neurotrophic actors, and peripheral nerve regeneration. Microsurgery 1998;18:397–405.
20. Lagoda G, Jin L, Lehrfeld TJ, Liu T, Burnett AL. FK506 and sildenafil promote erectile function recovery after cavernous nerve injury through antioxidative mechanisms. J Sex Med 2007;4:908–16.
21. Valentine H, Chen Y, Guo H, McCormick J, Wu Y, Sezen SF, Hoke A, Burnett AL, Steiner JP. Neuroimmunophilin ligands protect cavernous nerves after crush injury in the rat: New experimental paradigms. Eur Urol 2007;51:1724–31
22. Lagoda G, Xie Y, Sezen SF, Hurt KJ, Liu L, Musicki B, Burnett AL. FK506 neuroprotection after cavernous nerve injury is mediated by thioredoxin and glutathione redox systems. J Sex Med 2011;8:3325–34.
23. *Alkhayal S. and Lourdes M.*Corporeal Rejuvenation with Platelet Rich Plasma as a treatment for Erectile Dysfunction. Abstract (Poster) issmessm 2018, Lisbon.
24. Matz, E. Pearlman A. M., Safety and feasibility of platelet rich fibrin matrix injections for treatment of common urologic conditions. Investig Clin Urol. 2018

25. Epifanova, M.; Gvasalia, B.; Artemenko, S.; Durashov, M. First results of platelet-rich plasma and low intensity extracorporeal shockwave combined therapy for erectile dysfunction. Abstract (Poster) SMSNA 2019, Nashville TN.
26. Banno, J.J.; Kinnick, T.R.; Roy, L.; Perito, P.; Antonini, G.; The efficacy of platelet-rich plasma (prp) as a supplemental therapy for the treatment of erectile dysfunction (ed): initial outcomes. Abstract (Poster) SMSNA 2017, San Antonio TX.