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Title : The Effect of Combination Therapy Using Li-ESWT and PDE-5 Inhibitor Compared to PDE-5 Inhibitor Alone in Patients With Erectile Dysfunction

Date : December 1, 2019

Study Protocol and Statistical Analysis Plan

Study Summary

Title	The Effect of Combination Therapy Using Li-ESWT and PDE-5 Inhibitor in Patients With Erectile Dysfunction
Methodology	Randomized, controlled trial, blind study
Study Duration	Estimated duration for the main protocol (e.g. from start of screening to last subject processed and finishing the study) is approximately 9 months
Study Centre	Dr. Soetomo General Hospital, Surabaya - Indonesia
Objectives	To evaluate the effectiveness of combination therapy for mild to moderate erectile dysfunction using combination therapy (Li ESWT and tadalafil) versus tadalafil alone
Number of Subjects	30 randomized patients in two arms; test (combination therapy) and control (tadalafil monotherapy)
Diagnosis and Main Inclusion Criteria	Inclusion Criteria: • Mild to Moderate Erectile dysfunction • Married • Sexually active • Consenting to participate in the trial Exclusion Criteria: • Psychological problems • Spinal injury • History of malignancy • Penile anatomy abnormalities • Allergic and Contraindications to tadalafil • On anti-mitotic drugs
Study Product, Dose, Route, Regiment	Test group : receive tadalafil 2.5 mg once daily for 28 days combined with LiESWT twice weekly (energy density 0.09, frequency 5Hz, 600 pulse per location, in 5 locations : corpus penis distal, medial, and proximal, crux dextra et sinistra, 3 minutes of duration each location) Control group : receive tadalafil 2.5 mg once daily for 28 days
Statistical Methodology	EndPoint : Improve Erectile Dysfunction clinically, measured using Erectile Hardness Score and IIEF-5 (International Index of Erectile Function); Laboratory (measured using VEGF level); and Ultrasonographically (measured using PSV (Peak Systolic Velocity) of the blood flow in cavernous arteries)

Purpose :

To evaluate the effectiveness of combination therapy for mild to moderate erectile dysfunction using combination therapy (Li ESWT and tadalafil) versus tadalafil alone

Background :

Erectile dysfunction (ED) is defined as the inability to achieve and maintain penile erection sufficient for satisfactory sexual performance that last for at least three months. The majority of the cases are organic ED. And, to be specific, the origin of organic ED were due to vasculogenic causes, which the main culprit is thought to be the endothelial dysfunction.

PDE-5 Inhibitor is still the first line therapeutic options for this kind of ED. The mechanism of PDE-5 Inhibitor mainly to enable the vessels to dilate by inhibiting the PDE enzyme. Tadalafil is one kind of long acting PDE-5 Inhibitor. But still, some patients do not respond to the first line therapy.

Li-ESWT is generally Low intensity Shock Wave that is given Extracorporeal-ly. In this particular study, the site is the penis. Li-ESWT is thought to be able to induce angiogenesis which leads to the increase of PSV resulting increase in EHS and IIEF-5.

Addition of Li-ESWT regimen is expected to increase the respond of the standard PDE-5 Inhibitor therapy.

Goals of the study :

1. Improve Erectile Dysfunction clinically, measured using Erectile Hardness Score and IIEF-5 (International Index of Erectile Function); compared to the control group
2. To evaluate the angiogenesis effect laboratory (measured using VEGF level); compared to the control group
3. To evaluate blood flow in cavernous arteries ultrasonographically (measured using PSV (Peak Systolic Velocity); compared to the control group

Duration of the Study :

Duration for the main protocol (e.g. from start of screening to last subject processed and finishing the study) is approximately 9 months

Methods :

Study Design

Blind study involving thirty (30) subjects with mild to moderate erectile dysfunction will be placed in two randomized arms. One control group of fifteen (15) subjects will be given a standard first line therapy of tadalafil 2.5mg once daily. The other fifteen (15) subjects will be given a standard first line therapy, combined with LiESWT twice weekly (energy density 0.09, frequency 5Hz, 600 pulse per location, in 5 locations : corpus penis distal, medial, and proximal, crux dextra et sinistra, 3 minutes of duration each location).

Data will be collected manually from patient respons, and from radiology unit and laboratory. A dedicated hard-copy paper system specific to each patient will serve as secondary data collection. Each patient will be contacted by members of the research staff at each follow up point.

Study population and selection criteria

All aspects of the study and consents form will be IRB approved prior to implementation. All participants will require full informed consent, be willing and able to comply with all study requirements and will meet the following criteria; 40-55 years old, mild to moderate erectile dysfunction, married, sexually active.

Subjects will be excluded from the study based on the following criteria;

- Psychological problems
- Spinal injury
- History of malignancy
- Penile anatomy abnormalities
- Allergic and Contraindications to tadalafil
- On anti-mitotic drugs

Recruitment methods

Subjects are the new patients of Andrology Clinic of Dr. Soetomo General Hospital, with chief complaint of erectile dysfunction, categorized as mild to moderate, without any prior medication for the erectile dysfunction.

Data collecting and reporting

Data will be collected prior the therapeutic regiment, and after finishing the therapeutic regiment (28 days), consist of the EHS score, IIEF-5 Score, PSV value and VEGF level. EHS scores were obtained directly by asking the subjects after brief explanation. IIEF-5 scores were gained from the IIEF questionnaires which were filled by all subjects. PSV value based on the Doppler ultrasonography done by the radiology unit, and the VEGF level obtained from the blood test done by the laboratory.

Data of the study will be maintained for two (2) years after the investigation completed. A description of this clinical trial will be available on http://www.ClinicalTrials.gov

Expected outcomes

The expected outcome is improvement of the combination therapy is better than the standard therapy, clinically, and laboratory and radiologically.

Adverse reactions

There is no expectations of adverse outcomes or reactions due to patients treated with tadalafil and LiESWT. Possible adverse reactions of tadalafil as stated by the manufacturer already being infoermed to all subjects. Possible adverse reactions of LiESWT consist of pain in the impacted area has already been informed to all subjects. All participants will be given access to contact info of the PI, co-investigators, and andology clinic staffs. Any adverse reactions should be reported immediately.

Reasons for Withdrawal or Termination

A subject may be discontinued from the study at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

The following is a list of possible reasons for study treatment discontinuation:

- Screening Failure
- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Adverse Event that in the opinion of the Investigator would be in the best interest of the subject to discontinue study participation
- Protocol violation requiring discontinuation
- Lost to follow-up
- Subject death

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the Investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents and the Case Report Form (CRF). If a subject is withdrawn from treatment due to an AE (adverse Event), the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. The Investigator must make every effort to contact subjects who are lost to follow-up. Attempts to contact such subjects must be documented in the subject's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter, etc.).

Handling of Participant Withdrawals of Termination:

Although subjects may withdraw from the study at any time and for any reason, (or may be withdrawn at the Investigator's discretion), subject withdrawal should be avoided as much as reasonably possible. In any case, appropriate follow-up for endpoints should be continued. Subjects who prematurely discontinue are not to be replaced. For subjects considered lost to follow-up, the CRF must be completed up to the last visit performed.

Methods and Study Schedule:

Subjects eligible for the study will review and undergo informed consent. Once consented, subjects will be randomly assigned on a 1:1 basis to undergo:

- Test Group, blind:

    Tadalafil 2.5mg once daily, and LiESWT twice weekly regiment as described

- Control Group, blind:

    Tadalafil 2.5mg once daily as the standard first line therapy.

Baseline/Screening Visit (-2 days from Day 0 prior to therapy)

The following procedures will be performed at the Baseline/Screening visit:

- Review the study with the subject and obtain written informed consent and
- Assign the subject a unique screening/enrollment number
- Review and record medical history, surgical history, and medication history to determine eligibility based on inclusion/exclusion criteria
- Record demographics (age, race, ethnicity, gender)
- Document vitals

- Document all current medications, including medications over-the-counter and herbal medications
- Perform physical examination
- Assess IIEF-5 and EHS
- Perform blood VEGF test and Doppler ultrasonography

Treatment Visit (Day 0)

Control group (blind)

The fifteen (15) member of control group will receive three (3) tablets of tadalafil 2.5mg, to be taken once daily

Treatment Group (blind):

The fifteen (15) member of control group will receive three (3) tablets of tadalafil 2.5mg, to be taken once daily, plus the LiESWT procedure.

Folluw-up Visits

After initial treatment, all the subjects will have to follow the schedule for follow up at day 3, 7, 10, 14, 17, 21, 24

The following procedures will be performed at day 3, 10, 17, 24

Control group (blind)

The fifteen (15) member of control group will receive four (4) tablets of tadalafil 2.5mg, to be taken once daily, and assessment for adverse events and complications following treatments.

Treatment Group (blind):

The fifteen (15) member of control group will receive four (4) tablets of tadalafil 2.5mg, to be taken once daily, plus the LiESWT procedure, and assessment for adverse events and complications following treatments.

The following procedures will be performed at day 7, 14, 21

Control group (blind)

The fifteen (15) member of control group will receive three (3) tablets of tadalafil 2.5mg, to be taken once daily, and assessment for adverse events and complications following treatments.

Treatment Group (blind):

The fifteen (15) member of control group will receive three (3) tablets of tadalafil 2.5mg, to be taken once daily, plus the LiESWT procedure, and assessment for adverse events and complications following treatments.

Final Study Visit

The following procedures will be performed at the final post treatment visit at day 28:

- Assess for adverse events
- Assess for complications following treatments
- Perform physical examination
- Assess IIEF-5 and EHS
- Perform blood VEGF test and Doppler ultrasonography

Randomization

Subjects who meet all inclusion and exclusion criteria will be randomized on Treatment Day in a 1:1 ratio to either the Treatment Group or the Control Group, in accordance with a computer-generated schedule prepared by a biostatistician. Randomization will then be performed by the randomization personnel in charge. Study personnel will be instructed not to randomize until subject has been confirmed to meet all inclusion/exclusion criteria on treatment day.

SAMPLE SIZE JUSTIFICATION

Sample Size Calculations

$$n1 = n2 = \frac{2\,SD^2\,(Z\alpha + Z\beta)^2}{(x1 - x2)^2}$$

- SD = 10,5 (Vardi *et al.*, 2010)
- Zα = α 0,05 = 1,96.
- Zβ = β 0,10 = 1,28.

n1 = n2 = 10,2 → 11

Minimal sample for each group is eleven (11) subjects. Anticipation for drop-out was assumed 20%, adjusting the sample size calculation to fifteen (15) subjects for each group. Totalling thirty (30) participants.

STATISTICAL ANALYSIS PLAN

Endpoint

EHS score (Ordinal)

IIEF -5 score (Ordinal) measured from the standardized IIEF-5 questionnaire

VEGF level (Interval) obtained from blood test done in the lab

PSV (Interval) obtained from the result of Doppler ultrasonography done by the radiology unit

All analyses will be performed using per-protocol population.

EHS and IIEF-5 will be using median, VEGF ang PSV will be using mean.

For statistical analysis of comparisons were done using paired t test or Wilcoxon signed-rank test as appropriate for the between group pre and post test comparisons. As for between group experimental and control comparisons, independent t test or Mann-Whitney test were used as appropriate. Significance was set at 5% ($p < 0.05$). Statistical software used is EZR (Easy R)

ASSESSMENT OF SAFETY

Adverse events (AE) will be monitored and collected by the study team from the point of signed consent until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. For each AE, a detailed explanation will be obtained from the subject and subject's medical record. All AEs will be recorded on the CRFs.

Definition of Adverse Event

An AE is defined as any unanticipated medical occurrence regardless to relationship of the investigative arm of the trial. An AE can be any unintended sign, lab abnormality, symptom, or disease associated with the trial. Any abnormality that presents during a medical test are to be defined as an AE if it produces clinical signs and/or symptoms, requires intervention, or deemed clinically significant by the Investigator.

Definition of Serious Adverse Event

An adverse event is considered serious if it results in any of the following:

1. Death

2. A life-threatening AE

3. Requires inpatient hospitalization or prolongs existing hospitalization

4. Persistent disability/incapacity

5. Medically important event by the Investigator

Severity of Event

The Investigator will be asked to assess the severity of the AE using the following categories:

Mild:	Events require minimal or no treatment and do not interfere with the participant's daily activities.
Moderate:	Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe:	Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating

Expectedness

The Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study products.

Time Period and Frequency for Event Assessment and Follow-Up

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of

study participation. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

SAE Reporting

In the case of a SAE, the IRB must be notified according to their notification policies within one (1) day.

Data Safety Monitoring

As the treatments are currently being used as standard of care, the study team does not anticipate subjects experiencing any adverse events solely due to being in the study. This is simply a proposal to formally randomize and follow subjects undergoing two commonly performed procedures, both of which have been shown to be safe and approved. Therefore, a formal Data Safety Monitoring Board will not be needed for this study.

DATA MONITORING

The Principal Investigator will be responsible to ensure the study is conducted in accordance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and that the data recorded is valid. To achieve this objective, the study will be continuously monitored and reviewed on a monthly basis by the study team.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

A Clinical Monitoring Plan will be created by the IRB and describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

DATA HANDLING AND RECORD KEEPING

The collection of personal patient information will be limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.

Only study personnel will collect data. Hard copy documents will be retained for the duration of the study until data entry. All hard copy documents will be kept in a locked cabinet in the research coordinator's office (which will cover all the created CRFs) which will then be used for data analysis. Only de-identified data will be used for data analysis. All hard copy documents will be shredded within five years after completion of the study Collected de-identified data will be sent to a biostatistician for statistical analysis.

INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

CONSENT PROCESS

Subjects will be approached when they come through the clinic being evaluated and considered for therapy for mild to moderate erectile dysfunction. Each potential subject must provide written consent with full knowledge of the procedures involved. The informed consent, approved by the IRB and in accordance with regulatory guidelines, must be fully explained by the Investigator or member of the study staff including the study aims, methods, benefits and risks, and signed by the subject before enrollment into the study. Potential subjects will be informed that study participation is voluntary and that they may withdraw at any time. The subjects will be told that choosing against participation will not affect the care received for treatment. The subjects will be informed that they will be authorizing access of investigational staff to confidential medical records. The subject will be given sufficient time to read the consent and ask any questions. Once the informed consent is signed, the subject will be given a copy of the document.

PROTOCOL DEVIATION

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

All protocol deviations/violations should be documented using the Protocol Deviations/Violations CRF and submitted to the IRB according to their reporting guidelines.

LAWS AND REGULATIONS

This clinical study will be conducted in compliance with all national laws and regulations of the countries in which the clinical trial is performed, as well as any applicable guidelines. The trial will be registered on www.clintrials.gov and on other sites, as appropriate.

PUBLICATION AND DATA SHARING POLICY

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among investigators.

CONFLICTS OF INTEREST

No conflicts of interest have been reported.

STUDY PERSONNEL AND ROLES

1. **Andrian Japari, M.D. ; Principal Investigator**
2. **Androniko Setiawan, M.D. ; Co-Investigator**
3. **Rosy Nur Febriani, M.D. ; Co-Investigator**
4. **Tjahjo Djojo Tanojo, M.D. ; Study Coordinator**
5. **M. P. B. D. Pramesti, M.D. ; Study Coordinator**
6. **Agustinus, M.D. ; Project Manager**
7. **Dr. Budi Utomo, M.D. ; Data Manager**

APPENDIX I

The trial will be conducted in accordance with the Indonesian Health Research regulatory, and applicable to clinical studies (45 CFR Part 46, 21 CFR Part 91, 21 CFR Part 56, and 21 CFR Part 812). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signature Of Principal Investigator	Date (12/01/2019)
	
Printed Name	
Andrian Japari, M.D.	
Name of Institution	
Dr. Soetomo General Hospital	