PROTOCOL OF A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF MD IN OBSTETRICS & GYNAECOLOGY

Title of the Protocol: The Effect of Periurethral Injection of Platelet Rich Plasma Versus Mid-Urethral Sling in Treatment of Stress Urinary Incontinence: A Randomized Clinical Trial.

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What is already known on this subject? AND What does this study add?

Urinary incontinence can impact women's social, physical, mental and sexual wellbeing, and lead to depression and social isolation **(Sinclair et al., 2011)**. According to the International Continence Society, stress urinary incontinence (SUI) is defined as a complaint of urinary incontinence due to increased abdominal pressure, such as exercise, laughing, sneezing, and coughing **(Mørkved , Bo, 2014)**.

Treatment options include surgical and conservative methods. Among surgical procedures, mid urethral sling is a common and standard method for treating urinary incontinence in women **(Nikolopoulos et al., 2016)**.

The use of stem cells and other progenitor cells as injectable agents, offers potential alternative therapies. Another possibly effective simple method for the treatment of SUI is the combined use of injectable autologous compounds, in no context platelet-derived therapies are growing trend across multiple medical and surgical specialties **(Marx , Garg, 2005)**

This study aims to compare the efficacy of two minimally invasive treatments for stress urinary incontinence: periurethral injection of platelet-rich plasma (PRP) and mid urethral sling.

1- INTRODUCTION/ REVIEW :

Urinary incontinence (UI) remains a significant concern affecting women's quality of life globally. It has a significant impact on quality of life and creates personal and social financial burdens.**(Aoki et al., 2017)**.

Stress urinary incontinence (SUI) is defined by the International Continence Society (ICS) as "the complaint of any involuntary loss of urine on effort, physical strain, or when coughing or sneezing".**(Clavijo et al., 2021)**.

Although the exact etiology of SUI is unclear, common explanations include the absence of urethra coaptation, muscular compression of the proximal urethra, and stabilization of the bladder neck and proximal urethra that allows equal pressure transmission of increased abdominal pressure (**Pancho, 2020)**.

It is commonly acquired after pregnancy and childbirth due to weakening of the pelvic floor muscles that support the urethra against the anterior vaginal wall **(Buckley, Lapitan, 2010)**

Conservative and surgical treatments are among the conventional methods used to treat urinary incontinence. The conservative therapies include pelvic floor physiotherapy, biofeedback, electrical stimulation, and continence devices **(Dumoulin, Hay-Smith, 2008)**.

Among surgical procedures, mid urethral sling is a common and standard method for treating urinary incontinence in women. The mid-urethral sling (MUS) has become the preferred procedure, as it is less invasive than the Burch colposuspension **(Nitti, 2012)**. Although surgical techniques offer long-term treatments for SUI, they are not complication free. Surgical techniques may cause various complications, such as bleeding, bladder trauma, and urinary tract trauma, during the surgery or lead to delayed complications, such as pain, infection, urinary retention, bladder and urethral perforation, and vaginal erosion and extrusion **(Schimpf et al., 2014)**.

Another possibly effective method for the treatment of SUI is the use of injectable autologous compounds, which reconstructs the structure and function of ligaments surrounding the urethra and reduces surgical complications and high cost of stem cell application **(Marx, Garg, 2005)**. Many researchers have examined the reconstruction potential of blood components and plasma derivatives and proposed the use of autologous compounds including fibrin adhesive and platelet derivatives, such as platelet-rich plasma (PRP) and platelet-poor fraction (PPF) in low-cost tissue repair settings .**(Nikolopoulos et al., 2016)**.

PRP has gained significant popularity in various medical fields due to its regenerative capabilities, particularly over recent decades. PRP derived from the patient's blood, is renowned for its regenerative properties attributed to its high concentrations of growth factors and cytokines **(Dohan et al., 2009)**.

PRP therapy represents a minimally invasive alternative to surgery. This therapy involves injecting the patient's blood platelets into the urethral sphincter to stimulate regeneration and strengthen the muscle fibers **(Lee et al., 2021)**.

Recent reports showed that repeated injections of autologous PRP into the urethral sphincter are a safe and effective mid-term treatment for reducing the severity of female SUI by increasing urethral sphincter resistance as the studies repesented by **(Chiang, Kuo, 2022) (Clavijo et al., 2021)**.

2- AIM/ OBJECTIVES:

To evaluate the efficacy and safety of PRP in management of women with stress urinary incontinence in comparison to transobturator tape.

Research Hypothesis: Periurethral injection of Platelet-rich plasma (PRP) is safe and effective in treatment of women with stress urinary incontinence (SUI) in comparison to transobturator tape.

Study Question: Is PRP safe and effective in management of stress urinary incontinence in women in comparison to transobturator tape .

3- METHODOLOGY:

- **Type of the Study:** randomized control trial.
- **Study Setting:** Ain Shams University Gynecology and Obstetrics Hospital.
- **Study period:** till recruiting all sample size and finalizing results.
- **Study population:** women aged 26 – 66 years diagnosed with SUI seeking treatment.
- **Inclusion criteria:**
- Female patient with primary symptoms of SUI confirmed by patient's medical history and clinical symptoms, including a focused incontinence evaluation by simple cough stress test and urodynami study.
- Age 26 to 66 years.
- Patient's agreement to undergo surgical treatment.
- **Exclusions criteria:**
- History of previous surgical procedure for SUI.
- Malignancies of the genitourinary system.
- History of hemorrhagic disorders, anti-platelet agent treatment, uncontrolled diabetes mellitus.
- Recent history of genitourinary fistula or urethral diverticulum.
- Advanced pelvic organ prolapse on the pelvic examination.
- Any other contraindications for surgical procedures.
- Patient refuses to participate in the study.
- Evidence of detrusor over-activity on the urodynamic study.

- **Sample Size justification:** Assuming an effect size for the difference in stress incontinence measured by a specific questionnaire of 0.8, a sample of 21 patients in each group would be enough to detect such effect , if true , at 0.05 alpha level and 0.80 power of the test with an expected drop out rate of 15% each group will include 24 patients.**(Daneshpajooh et al., 2021)**
- **Sampling method:** computer generated sampling.
- **Study Procedures:** Discussion about the study with explanation of benefits, and risks, and informed consent will be obtained. "Appendix I".

The baseline characteristics will be recorded according to Case Report Form (CRF).

"Appendix II".

Participants will randomly be assigned to one of the following groups:

- **Platlet rich plasma group.**
- **Transobturator tape group.**

A. <u>Periurethral PRP injection group (Long et al., 2021):</u>

(21) patients will receive periurethral PRP injection.

The patients will be discharged after ensuring their full recovery and stable clinical condition

The patients' responses to the treatments will be evaluated one and three months after the treatments, using ICIQ questionnaire, and cough stress test.

B. <u>Transobturator tape group:</u>

(21) patients will receive a standard transobturator tape.

o **PRP preparation method:**

Venous blood (15 mL) will be stored using acid citrate dextrose (ACD) anticoagulant, and falcon tubes (15 mL) will be centrifuged for 10 minutes at 800 rpm. After separation of PRP, which will be deposited on red blood cells, it will be transferred into new 15-mL falcon tubes. They will be then centrifuged for 15 minutes at 3500 rpm, and platelet concentrates will be prepared by removing the platelet-poor plasma supernatant.

- **PRP injection method:**

The patients will be placed in a dorsal lithotomy position. The vagina will be prepared and draped .The procedure will be done with local anaesthia ,we will perform a periurethral block with 2% lidocaine. Approximately 4 mL of the platelet concentrate will be deployed by injections performed retrograde(periurethral) by a 5 cc syringe with 30 G needle into anterior vaginal wall at mid urethra. **(Clavijo J et al., 2024)**

- **All patients work up**:

o **Detailed history**:

It includes personal (name, age), present, obstetric history (number of parity, mode of delivery), medical, surgical, gynecologic, and neurologic histories also should be obtained. Certain medical and neurologic conditions, such as multiple sclerosis, diabetes, stroke, and lumbar disk disease, may precipitate urinary incontinence.

The purpose of history taking is to help determine the type of urinary incontinence. History should include characterization of incontinence (eg, stress, urgency, mixed), duration, precipitating events, fluid intake, frequency of occurrence, interference with activities of daily life, severity, pad use, and effect of symptoms on activities of daily living. Physicians will use validated questionnaires to evaluate incontinence by International Consultation on Incontinence Questionnaire-Short Form (ICIQ) and Incontinence quality of life questionnaire (I-QOL).

o **Complete physical examination:**

The primary purpose of the physical examination is to exclude confounding or contributing factors to urinary incontinence or its management. It is recommended that all pelvic support compartments (anterior, posterior, and apical) be assessed in women with urinary incontinence symptoms. .Prolapse can mask or decrease the severity of the woman's incontinence symptoms, especially stress incontinence symptoms; this is referred to as occult, potential, masked, or hidden stress urinary incontinence.

General examination: Including height, weight and BMI), abdominal examination (including scar of any operation).

Local examination:

Inspection, vaginal examination, speculum and bimanual examination, cough stress test. Visualization of fluid loss from the urethra simultaneous with a cough is a positive test diagnostic of stress urinary incontinence. The cough stress test can be performed in the supine position during the pelvic examination. However, if urine leakage is not observed in the supine position, the test should be repeated with the patient standing and with a full bladder (or at a minimum bladder volume of 300 mL) to maximize sensitivity.

- **Investigation:**

CBC, urine analysis, urine C&S, urodynamic study through valsalva Leak point pressure (VLPP).

Follow up:

The patients' responses to the treatments will be evaluated one and three months after the treatments, using ICIQ questionnaire, and cough stress test.

• **Outcomes:**

- ***Primary outcome:***
  - Objective assessment of urinary incontinence by Cough stress test.
- ***Secondary outcomes:***
  - The change of the subjective assessment by the International Consultation on

Incontinence Questionnaire-Short Form Incontinence o Level of discomfort during injections and any adverse events are also evaluated.

Ethical Considerations:

- The data collected will not include any identifying information (personal identifiers, audio recordings, video recordings).
- The study will be conducted in accordance with the current Ain Shams University IRB approved regulations and requirements.

The investigator will be certain that an appropriate informed consent process is in place and that participants are fully informed of the nature and objectives of the work and of their rights to withdraw from that study without affecting the medical care to them.

• **Protocol approval:**

o Before the beginning of the study and in accordance with the local regulation, the protocol and all relevant documents will be approved by the Board of Department of Obstetrics and Gynecology, Ain Shams University and by the Research Ethics Committee, Faculty of Medicine, Ain Shams University.

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