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CASE REPORT

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Mixed treatment for same-severe mixed urinary incontinence: A novel method

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Key Clinical Message

Innovative mixed treatment offers hope for persistent mixed urinary incontinence (MUI): PRP-Fibrin Glue-Stem Cell injection, Botox, and TVT in a single session. Successful case study reveals promising outcomes, emphasizing the need for further research.

Abstract

Mixed urinary incontinence is a complaint of stress and urge incontinence which affects patients' quality of life and dramatic changes in patients' physical, mental, and socioeconomic status. The treatment is challenging and depends on the dominance of one of the complaints to the other. The progress in the method of treatment is still under discussion. This study reports treatment of a MUI case in a 56-year-old, with a history of MUI of 7-year duration, which was persistent to pharmacological treatment, pelvic muscle training, biofeedback, and anti-incontinence surgery (Burch Colposuspension). PRP-Fibrin Glue-Stem Cell injection, Botox injection, and TVT were performed in a one surgery session. Patient was discharged with ability to urinate with acceptable amount of post void residue. After 3-month follow-up, patient was completely satisfied and happy. Further research is needed to substantiate the efficacy of these mixed treatments for MUI.

KEYWORDS

novel treatment, platelet-rich plasma, stem cells, treatment efficacy, urinary incontinence

1 | INTRODUCTION

International continence society defined mixed urinary incontinence (MUI) as "complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion and on sneezing or coughing", which include both urgency urinary incontinence (UUI) and stress urinary incontinence (SUI) complaints. Urinary incontinence has been found to have a significant impact on various aspects of individuals' lives, including social behaviors, financial implications related to the need of pharmaceutical interventions, the need for rehabilitation of pelvic floor muscles, and psychological distress, particularly in relation to sexual dissatisfaction. The diagnosis

of urinary incontinence relies on a comprehensive assessment that includes a thorough medical history, physical examinations, and additional diagnostic procedures such as dye tests, cystoscopy, urodynamic studies, urine analysis, urine culture, and imaging techniques.[1]

Initially, conservative treatments are administered to patients, such as biofeedback, pelvic floor muscle exercise, electrical stimulation, and pharmacological therapy. During the second phase of the therapy process, surgical intervention is taken into consideration. The surgical procedure is commonly employed to treat the inadequate anatomical support of the bladder neck and proximal urethra, as well as intrinsic sphincter deficit. However, it is important to exercise caution and approach its implementation with careful consideration. In certain instances, surgical intervention may prove ineffective, necessitating the exploration of other therapies.[2]

The application of platelet-rich fibrin glue, stem cells, botulinum toxins, and tension-free vaginal tape (TVT) has been previously reported for the treatment of individuals. However, this study represents the first instance in which these combined modalities were utilized for the management of mixed urine incontinence that exhibited resistance to both pharmacological and surgical interventions. Highlighting positive outcomes in the presented case study may foster understanding of PRP's potential benefits for MUI. Advocating for further research and clinical trials could eventually lead to its inclusion in insurance coverage, enhancing accessibility for patients.

2 | CASE

A 56-year-old multiparous female was referred to the clinic with complaint of MUI for 7-year duration. She had six normal vaginal deliveries and a history of disk surgery and Burch colposuspension. She suffered from nocturia and terminal dribbling. She had a history of six natural vaginal delivery, spinal surgery on L4 and L5 vertebrae after several years suffering from lumbar discopathy, and a gall bladder surgery 2 years before presentation. Oxybutynin, vesicare (Solifenacin Succinate), and amitriptyline were administered without any improvement. Pelvic muscle training and biofeedback method were performed followed by anti-incontinence surgery Burch Colposuspension 3 years ago; however, these did not improve the patient's condition. The patient did not have burning sensation indicative of urinary tract infection, also no flank or supra-pubic pain. Voiding diary showed frequent episodes of incontinence during day and night. On the physical examination, no vaginal prolapse was detected due to previous Burch Colposuspension. Kidney ultrasound evaluation was normal. Urodynamic study showed high intravesical pressure, and episodes of urge incontinence and interchange UPP and (urethral profile pressure) showed sphincter deficiency. Abdominal leak point pressure (ALPP) was 62 cm H_2O. Cystoscopy showed fixed open internal sphincter with normal capacity and moderate urinary bladder tribulations.

Informed consent was obtained from the patient. Risks and benefits, and the right to withdraw at any point was mentioned for the patient. At the baseline, 1 and 3 months after intervention, the patient were assessed according to cough test, pad test, urodynamic study, upper tract ultrasonography (UTU), uroflowmetry (UFL), post voiding residue (PVR), International Consultation on Incontinence Questionnaire-Urinary incontinence (ICIQ-UI), and International Consultation on Incontinence Modular Questionnaire-Quality of Life (ICIQ-QOL).

For patient, platelet-rich plasma-fibrin glue-stem cells injection, botulinum toxins injection, and TVT were applied in one session of surgery under general anesthesia.

2.1 | Preparation of autologous platelet-rich plasma-fibrin glue-stem cell

Sixty milliliters of peripheral blood was taken in 9 mL of citrate phosphate dextrose buffer. Platelet-rich plasma (PRP): blood was centrifuged at 2000 *g* for 2 min, red blood cell (RBC) and plasma were separated, and plasma was centrifuged at 4000 *g* for 8 min, and the supernatant plasma was separated and 4 mL PRP was separated. Fibrin glue (cryoprecipitation method): The supernatant plasma was frozen at −80°C, thawed and centrifuged at 4000 *g* for 8 min. The supernatant plasma was separated to a final volume of 4 mL. Platelet count, aggregation, and pH measurements on days 1 and 3 of storage and microbiological tests were carried out on the fifth day of storage in order to ascertain the safety of the product. Stem cell: hydroxyethyl starch was added to RBC and left for 45 min RBC sedimentation. Supernatant was separated, centrifuged 400 *g* about 10 min, and supernatant was removed to final 4 mL volume. Bacterial tests and endotoxin levels were assessed before the administration of the drug to ensure the safety and sterility of the medical product.[3]

2.2 | Platelet-rich plasma-fibrin glue-stem cell and botulinum injection

In operation room, the patient was under general anesthesia and lithotomy position. PRP, fibrin glue, and stem cell were mixed (12 mL) before injection. The transurethral endoscopic injection of PRP-Fibrin glue-stem cell was carried out by a 21-Fr rigid cystoscope. Under endoscopic

vision, a puncture needle was passed through the cystoscope into the urethra at the region of the external urethral sphincter and submucosal injections of PRP-Fibrin glue-stem cell was performed. Initially, 8 mL was injected at a depth of 5 mm into the rhabdosphincter. Subsequently, 4 mL was equally injected into the submucosal spaces at 3 and 9 O'clock positions. Hundred unit of botulinum toxin was injected via cystoscope into vesical detrusor.

2.3 | Tension-free vaginal tape

Sixty milliliters of Citanest-Adrenalin (0.25%) was injected in the abdominal skin just above the pubis symphysis and retzius space. After 2 cm long transverse skin incision, 40 mL of 0.25% Citanest-Adrenalin was injected into the vaginal wall sub- and paraurethrally. 1.5 cm long incision in the midline starting approximately 0.5 cm from the outer urethral meatus in the vaginal wall. Laterally, a blunt dissection 1.0 cm long was made on each side of the urethra. A sling was placed around the urethra using a needle: It was inserted into the prepared paraurethral incision on the right side of the urethra. The urogenital diaphragm was perforated and the tip of the needle was brought up to the abdominal incision by "shaving" the back of the pubic bone. The procedure was then repeated on the left side. When the sling had been placed in a U shape around the midurethra, owing to the strong adhesive forces (friction) around the sling no fixation was necessary. The vaginal incision was then closed. A folly catheter was inserted.

3 | OUTCOME

3.1 | Results

No complications were observed after injection. After surgery, the patient had compression device for 24 h, and then, she was motivated to walk gently. Catheter was removed the following day after surgery. Patient was discharged from hospital with the ability to urinate and acceptable post void residue. In this surgery, the utmost effort was done to minimize the vaginal bleeding in order to not apply the vaginal tampon for preventing the damage to stem cells. After 3-month follow-up, patient was completely satisfied and her problem was completely sorted out. At the baseline, cough test and pad test were positive; UTU, UFL, and PVR were normal; ICIQ-UI and ICIQ-QOL were 21 and 24, respectively. At 1 and 3 months after intervention, cough test and pad test were negative; UTU, UFL, and PVR were normal; ICIQ-UI and ICIQ-QOL were 0 and 104.

After the recovery, she was observed 1 day in female urology ward and next day was discharged with prescription. After 3 months, the incontinence was completely cured and patient had no urinary complaints.

4 | DISCUSSION

A single modality may be inadequate for treatment of MUI and multiple treatment modalities are required. There is a controversy about the results of pharmaceutical treatment for MUI and surgical treatment is associated with significant failure rates. It is mentioned that applying of anti-incontinence procedures may be effective in treating both the stress and urge components of MUI.[4]

American urology association (AUA) reported "the success rate of TVT surgery is between 51% and 87%".[5] Labire et al.[6] expressed that the pharmacological therapy is less effective in comparison to surgery after 12 months. Surgery is done for those patients who decline conservative managements or whose symptoms have not improved adequately.[1] Kulseng-hanssen et al.[7] reported that "the TVT objective care was 87.3% after 7 months and 82.7 after 38 months. The subjective care was 60% and 53.8% after 7 and 38 months, respectively."

Botulinum toxin is a neurotoxin which has been used for various clinical applications for many years, and inhibits the release of the neurotransmitter acetylcholine at the presynaptic nerve terminals. Urologists use it for patients with lower urinary tract symptoms secondary to idiopathic overactive bladder (OAB) and also after initial therapeutic modalities have failed to improve symptoms. Intradetrusor botulinum toxin injection has shown to improve urinary urgency, frequency, nocturia, and UUI. On the other hand, not all patients can achieve excellent therapeutic outcomes which is due to leakage associated with a rise in abdominal pressure, for example, as a result of, excessive cough, sneeze and exercise.[8] Phelan et al. reported that after injection, 67% of patients were able to void smoothly with the PVR decreased by 71% and voiding pressure decreased by 38%.[9]

For tissue regeneration of muscles, stem cells, PRP, and fibrin glue strongly collaborate together to create new blood vessels and capillaries, extracellular matrix through cell proliferation, chemotaxis, cell differentiation, and angiogenesis. PRP provides the best concentration of growth factors (transforming growth factor–β, platelet-derived growth factor, insulin-like growth factor, fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor, and endothelial cell growth) Additionally, bioactive substances such as serotonin, histamine, dopamine, calcium, and adenosine play a role in these processes. These factors contribute to the process of wound healing by regulating the recruitment, proliferation, activation, and differentiation of cells involved in

the healing process. Fibrin Glue (FG) creates a temporary matrix and stimulating the local proliferation of fibroblasts, collagen synthesis, new blood vessels formation and connective tissue.[3] The malfunction old cells will be replenished by stem cells which these young workers actively collaborate in vascularization and muscle tissue repair. In our previous report, peripheral stem cells and PRP are used for the treatment of SUI.[10]

In this case report, PRP-Fibrin Glue-Stem Cell injection, Botox injection, and TVT have been used for the treatment of MUI. Further research is needed to validate the efficacy of these mixed treatments for recalcitrant MUI.

5 | CONCLUSION

Mixed treatment of PRP-Fibrin Glue-Stem Cell injection, Botox injection, and TVT may be a very good approach for the treatment of patients with MUI who have a very open sphincter. Further research is needed to validate the efficacy of these mixed treatments for recalcitrant MUI.

AUTHOR CONTRIBUTIONS

Daryoush Hamidi Alamdari: Conceptualization; project administration; writing – original draft. **Armina Douzandeh:** Conceptualization; methodology. **Maliheh Keshvari Shirvan:** Investigation; supervision. **Behzad Narouie:** Data curation; supervision. **Negar Radpour:** Data curation; methodology.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interest regarding the publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DISCLOSURE

All human subjects provided written informed consent with guarantees of confidentiality. The authors are employed at an academic or research institution where research or education is the primary function of the entity.

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