REVIEW ARTICLE

Novel Therapies in Management of Stress Urinary Incontinence

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Abstract

Female urinary incontinence (UI) is a common problem affecting 40% of women, but it is usually understated. It not only is a medical problem but has a larger impact on a women's social and psychological life. It is often not reported by women especially Indian women as they tend to accept it as a part of aging or a consequence of childbirth. In this review, we would be focusing on female stress UI (SUI) and newer therapies that can help improve the symptoms and lifestyle of such women. Pregnancy, childbirth, menopause, obesity, advanced age, and race and ethnicity are some common risk factors for SUI. The underlying mechanism includes pudendal nerve denervation, loss of ligamentous support of the urethral complex leading to dysfunction of the levator ani muscles, endopelvic fascia, and muscular urethra causing UI. Many treatment options are available for treating UI, such as lifestyle changes, pelvic floor muscle training (PFMT), bladder training, and electromagnetic stimulation of the pelvic floor muscles, and the surgical procedures—Burch colposuspension and bladder-neck slings and their various modifications. Traditionally, surgery forms the mainstay of management but now focus is towards minimally invasive and non-surgical techniques which could improve the quality of life in such patients. Newer therapies for SUI Management includes the drug-duloxetine, laser therapy and stem cell therapy.

Keywords: Genital prolapse, Incontinence, Levator ani, Menopausal problems, Pelvic floor dysfunctions, Pelvic floor muscle exercise, Pelvic organ prolapse, Stress, Urodynamic studies.

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Introduction

In females, urinary incontinence (UI) is one of the common presentations in outpatient department. It affects 40% of women, but it is usually understated.[1] It not only is a medical problem but has a greater impact on a women's social and psychological life. It is often not reported by women especially Indian women as they tend to accept it as a part of aging or a consequence of childbirth. It is only when it is symptomatic enough that women of our country would actually consider it as a disease needing physician consultation. The International Continence Society and International Urogynecology Association defined UI as a condition in which involuntary urine loss occurs. Various risk factors for incontinence are advanced age, multiparity, recurrent vaginal delivery, increased body mass index, menopause, pelvic trauma, constipation, chronic disease (diabetes), and history of gynecological and pelvic surgery also increases the risk.[2] The underlying mechanism includes denervation of pudendal nerves, loss of ligamentous support of the urethral complex leading to dysfunction of the levator ani muscles, endopelvic fascia, and muscular urethra causing UI.

Urinary incontinence can present as stress UI (SUI), urge UI (UUI), and mixed UI (MUI). The SUI is the most prevalent type. It is defined as incontinence during physical activity that increases intra-abdominal pressure, such as coughing, sneezing, or laughing. Urge incontinence, on the contrary, is urgency to pass urine, with frequency, and nocturia. It is also known as overactive bladder (OAB) syndrome and is due to detrusor overactivity. The MUI refers to urine leakage with a combination of SUI and UUI and is often difficult to treat with the available pharmacologic and nonpharmacologic treatments.[3–7]

In this review, we would be focusing on SUI and newer therapies that can help improve the symptoms and lifestyle of such women.

The various options for treating UI are lifestyle changes, pelvic floor muscle training (PFMT), bladder training, and electromagnetic stimulation of the pelvic floor muscles, surgical procedures, such as Burch colposuspension and bladder-neck slings, and their various modifications.[3] Traditionally, surgery forms the mainstay of management but now focus is toward minimally invasive and nonsurgical techniques, which could improve the quality of life in such patients. Yet, none is effective in treating SUI as nonsurgical procedures are usually not effective and the rate of complications with such procedures is relatively high, ranging from perioperative trauma, injury, hemorrhage, pain, infection, urinary retention, and foreign body reaction to the implant.

In 2014, the American College of Obstetricians and Gynecologists released guidelines for the evaluation of uncomplicated SUI in women before surgical treatment is advised.[6] It lays down six steps that are to be followed before opting for surgical management. The initial step is taking a detailed history followed by urinalysis. After this, a physical examination needs to be performed and a cough test to demonstrate SUI. The next step is evaluation of urethral mobility by the help of various tests and the final step involves measurement of postvoid residual volume. This detailed evaluation of patients helps us to reach the best possible treatment that can be given.

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Newer therapies for SUI management includes duloxetine, laser therapy, and stem cell therapy.[5]

Duloxetine

Duloxetine is a serotonin and norepinephrine reuptake inhibitor. It does not have affinity for histaminergic, dopaminergic, cholinergic, and adrenergic receptors. It inhibits the presynaptic reuptake of 5-hydroxytryptamine (5-HT) and norepinephrine (NE) in Onuf's nucleus of sacral spinal cord, thereby increasing their concentration in the synaptic cleft. It is the only pharmacological drug beneficial for SUI. It has been used in the past for the treatment of depression and peripheral neuropathy pain. The most common side effect is nausea. It is contraindicated in pregnancy, lactation, and liver disease. The recommended dosage is 40 mg twice a day. It should not be used in combination with monoamine oxidase inhibitors due to the risk of serotonin syndrome, CYP1A2/CYP2D6 inhibitors, as it can lead to increased concentration of the drug. The drug should be gradually withdrawn over 2 weeks as it can precipitate withdrawal symptoms.[8–10]

The efficacy of duloxetine in SUI was first studied by Thor and colleagues in a cat model of bladder irritation.[8] It was found that administration of duloxetine leads to a dose-dependent increase in bladder capacity and enhanced periurethral striated muscle activity. However, duloxetine did not affect bladder contractions caused by direct electrical stimulation (ES) of efferent fibers in the pelvic nerve, leading to the supposition that its effects are due to central rather than peripheral mechanisms. These studies in animal models led to further exploration in human subjects.

In a double-blind placebo-controlled study undertaken by Cardozo et al., a significant reduction in frequency of incontinence episodes was observed. Duloxetine 60 mg twice a day was administered in women suffering from severe SUI and awaiting surgery. Twenty percent of patients treated with duloxetine were no longer interested in surgery following the 8-week treatment phase compared to none in the placebo group ($p = 0.001$).

A study conducted by Ghoneim et al. compared duloxetine and PFMT, alone and in combination for treatment of SUI. A total of 201 women aged 18–75 years were included, with predominant symptoms of SUI. The median incontinence episode frequency (IEF) reduced by 57% in duloxetine alone or duloxetine in combination with PFMT group in comparison to PFMT alone group where only 35% reduction in IEF occurred (29% reduction with no treatment). The mean total incontinence quality of life questionnaire (I-QOL) score was increased by 13.1, 8.3, 7.8, and 4.8, respectively, with combination therapy, duloxetine alone, PFMT alone, and no treatment. The median decreases in pad use were for the combination, 46%; for duloxetine alone, 35%; for PFMT alone, 25%; and for no treatment, 10%. This study showed that duloxetine (80 mg daily) was better than placebo in terms of subjective cure and improvement in incontinence, though the estimated effect on cure was modest—only about 3% extra patients cured. Most participants in the duloxetine groups reported an adverse effect. Around 12% of these could be directly attributed to duloxetine because over half in the placebo group also reported adverse effects. In the duloxetine group, 17% stopped treatment, wherein about 75% of them attributed the reason to duloxetine. This is a higher rate compared to the trials of anticholinergic treatment of OAB symptoms. This adverse effect profile was judged to be acceptable by the authors of the trial reports.

In a meta-analysis of four randomized placebo-controlled trials of duloxetine ($n = 1,913$), it was found that duloxetine was better than placebo in terms of percentage change in weekly incontinence episodes [mean difference −13.56%, 95% confidence interval (CI) −21.59% to −5.53%] and change in incontinence quality-of-life total score (mean difference 3.24, 95% CI 2.00–4.48). The effect sizes were small, and a sensitivity analysis (with removal of one trial) showed that the number needed to treat a Patient Global Impression of Improvement rating of "much better or very much better" was 8 (95% CI 6–13). The numbers needed to harm were 7 (95% CI 6–8) for discontinuing because of an adverse event and 7 (95% CI 6–9) for experiencing an activation event. No adverse events such as suicidal ideation and akathisia were noted. Duloxetine was found to be effective for SUI in women, but when individual patient data were analyzed, the harms outweighed the benefits.[11–13]

Surgery seems to be more cost-effective over duloxetine. Many randomized controlled trials show significant treatment benefits in women taking duloxetine. However, relatively high incidence of adverse effects with duloxetine increases the rate of discontinuation. It is a good option in women awaiting surgery or those who are otherwise unfit for surgery. Duloxetine still continues to be in the gray zone for the management of SUI, as no study has completely eliminated the risk of major adverse events. It has been approved by the European regulatory agencies but Food and Drug Administration (FDA) approval is still lacking. If approved, it will be the first ever drug to be used for the treatment of SUI.

Laser Therapy

Laser had been studied in animals and humans and can cause collagen remodeling. This property is being utilized by plastic surgeons for skin rejuvenation and reconstruction. Two distinctive laser types are the microablative fractional CO_2 laser and the nonablative photothermal erbium-doped yttrium–aluminum–garnet (Er:YAG). CO_2 laser was first used for the treatment of genitourinary syndrome of menopause and female UI.[14–19] The wavelength of CO_2 laser used is 10600 nm which penetrates a depth of 50–125 µm vaginal tissue. The energy released causes contraction of the underlying vaginal layers. The Er:YAG has a wavelength of 2940 µm. At this wavelength, thermal effect can reach up to a depth of 5–20 µm. Thermal energy helps in both shrinking and tightening of the vaginal and pelvic floor tissues, which subsequently results in greater support to the bladder and urethra. This process of collagen remodeling is not transient following laser exposure but lasts for at least 6 months.[12] Laser treatment is completed in three phases: first, a full-field handpiece with a 360°-circular adapter is used to perform irradiation of the vaginal canal for two passes. Second, a handpiece with a 90°-angular adapter is used to deliver fractionated smooth beam perpendicularly to the anterior vaginal wall, lifting the bladder due to shrinkage of anterior vaginal wall. On the completion of the second phase, the laser speculum is removed from the vaginal canal and laser energy is delivered to the mucosa of the vestibule and introitus, by direct irradiation with fractionated smooth beam in three passes. Third a fractional handpiece and straight-shooting tip is used, consolidating the ligaments and connective tissues around urethra. It is also used to shrink the introitus of the vaginal canal. Around 1000 J of energy is deposited to the vaginal mucosa in one cycle of treatment, raising the temperature to usually >60°C. First session is followed by a second session after 4–6 weeks and the third session is performed 6 months after the first procedure. The advantages are that the procedure is done without an incision and is virtually painless. Recovery is extremely quick, i.e., no need for the use of antibiotics or analgesics. It is a relatively easy process,

i.e., only some preoperation tests and examinations required. Mild or even moderate cases are usually treated in two sessions. It also does not need any special preoperation or postoperation precautions, with the patients immediately returning to their daily activities. No adverse events have been noted in any of the studies performed till date. Data from most studies suggest that about 70% of women are dry after 4 months.[14]

Pergialiotis et al. undertook a systemic review on the role of laser therapy to vagina as a treatment option for SUI[15] ($n = 760$). They could not find any randomized control trials and it was found that the methodological quality of the reported studies was low. Reported studies had several limitations such as statistical bias, methodological flaws, the lack of a control group, or comparison with other clinically proven treatment modalities. It was, thus, concluded that there is lack of firm evidence to recommend laser therapy for SUI management.

In 2018, Okui conducted a comparative study in Japanese women, comparing laser therapy and sling procedures [tension-free vaginal tape (TVT) and transobturator tape (TOT)] for treatment of SUI. The 1-hour pad test, the International Consultation on Incontinence Questionnaire short form (ICIQ-SF), and OAB symptom score were used to assess the patients before and 12 months after the treatment. The TVT, TOT, and laser therapy groups showed comparable improvements in SUI; but for patients with MUI, some in the TVT and TOT groups showed exacerbation; however, all patients in the laser therapy group tended to improve. The efficacy of laser therapy for UI was confirmed.

The first ever randomized controlled trial was performed by Blaganje et al. ($n = 114$).[17] The premenopausal parous women with SUI were randomized in two groups: a laser intervention group and a sham group. Both groups were treated according to the IncontiLase® clinical treatment protocol for SUI with nonablative thermal-only Er:YAG laser, except that there was no energy output when treating the control group. Three months after the treatment, the laser group showed improvements in ICIQ-UI SF, all perineometer variables, duration, and maximum pressure, whereas the average pressure did not show any improvement as compared to the sham group. Twenty-one percent of laser treated patients were dry at follow-up compared to only 4% of the sham control patients. No serious adverse effects were observed or reported. It was concluded that laser therapy provides a promising minimally invasive safe treatment alternative for SUI.

The Urological Society of India in its 2018 backed up the clinical research of intravaginal laser for management of SUI, which cannot be currently recommended due to the limited and small studies.[5] At present, worldwide about 15 companies are in the process of marketing and promoting vaginal laser treatment for a range of urogenital symptoms. But conclusive evidence is still lacking. Laser is costly, and lack of long-term safety appears to be a setback for this modality. Randomized control studies are required to objectively define the role of laser therapy in SUI.

Stem Cell Therapy

Stem cells can differentiate in different lineage and have the capacity of self-renewal. Bioactive factors are released at the site of injury, which direct other stem and progenitor cells to the area of injury. These biofactors have antiapoptotic, antiscarring, immunomodulatory properties and help in neovascularization. Autologous muscle-derived stem cells (MDSCs) have been injected directly via either transurethral or periurethral route. For some years, stem cell therapy is being done for the treatment of nonurological disorders, but for urological diseases, or more specifically, incontinence, more basic science research comparing the type of cells, dosages, timing of optimal dose or doses after injury, mechanism of action of stem cells, and route of administration must be performed. Local periurethral injections of stem cells have all yielded successful outcomes in animal models of mechanical, nerve, or external urethral sphincter injury in SUI.[20–23]

In one of its first type of study to use MDSCs in the treatment of incontinence by Carr et al. in 2008,[14] eight SUI female patients who did not improve on other noninvasive treatment of incontinence for at least 12 months were recruited. The MDSCs were isolated from the thigh and $18–22 \times 10^6$ cells were transurethrally injected. A significant improvement was observed in 75% of SUI patients 12 months after treatment. The remaining 25% patients showed a reduction in incontinence episodes by approximately 50% based on pad weight. Later in 2013, the study was expanded to include 38 women with SUI who were treated with low or high doses of autologous MDSCs.[24] Authors showed a 50% or greater reduction in pad weight and diary reported stress leaks after cell therapy. This result was achieved more frequently in patients with high cell dose injections than in patients treated with low cell doses. These data suggest that high cell dose injection is better than a low cell dose in SUI.

Study by Blaganje et al.[16] demonstrated the efficacy of autologous myoblast samples isolated from a biceps muscle used for injection under transurethral ultrasound guidance into the external urethral sphincter of 38 female patients followed by ES. Additionally, the effects of the myoblast injections followed by an ES cycle were compared to those of a preoperative ES cycle undergone by the same patients. No serious adverse events or complications were noted and the procedure was well tolerated. Compared with the objective and subjective measurements collected immediately after the preoperative ES cycle, the measurements obtained 6 weeks postoperatively indicated considerable improvement. The results of the stress test were negative for 78.4% of the patients, 13.5% considered their SUI cured, and 78.4% reported improvement. They concluded that intrasphincteric autologous myoblast injections followed by ES is minimally invasive, feasible, and safe.

The largest study using stem cells for treatment of SUI female patients was published in 2014 by Peters et al.[18] Their study included 80 females who were divided into four different autologous MDSC dose groups (10×10^6, 50×10^6, 100×10^6, and 200×10^6). No difference was found between transurethral or periurethral approaches. A significant reduction was observed in the diary reported stress leaks at 12 months in all dose groups within 1–3 months of cell therapy, unlike after 12 months of follow-up when a greater percentage of patients were responsive to higher doses.

Overall this mode of treatment is easy to perform, is minimally invasive, and involves no complications such as hematoma formation, urinary retention; but it is yet to become a mainstream therapy as optimal timing and route of administration have not been determined. Also, the long-term safety of stem cells is yet to be elucidated. There are very limited sources in literature of stem cell therapy in the management of SUI.

Conclusion

Initial management involves a variety of noninvasive interventions. Pharmacological treatment is not effective in all women especially with severe symptoms. Surgery is safe and effective but is

invasive with complications. Duloxetine is widely used for pain management, anxiety disorders; however, its use in SUI is still not FDA approved and uncertainty exists with respect to its role in SUI. Stem cell therapy is promising, but long-term results are awaited. Studies have proved that laser treatment using Er has shown score improvements in ICIQ-UI SF, superior changes in perineometer measurements, and decrease in Q-tip angle and also a better quality of life post 6 months' treatment. Laser treatment of SUI seems to be the most important discovery in the nonsurgical management of SUI. However, as discussed above, long-term studies recommending its routine use are still lacking.

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