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Current Controversies in Stem-Cell Treatment of Urinary Incontinence in Women

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Abstract

Background: Urinary incontinence (UI) is a major cause of morbidity in the world and is believed to affect up to 46% of the female population Our objective was to analyze the papers that describe stem-cell treatments for UI in women.
Methods: We performed a systematic review of the literature from 1946 to date that reports on clinical trials that use stem cells to treat women with urinary incontinence.
Results: Nine articles (7 observational and 2 randomized studies) met the inclusion criteria. No major adverse effects were observed in any of the studies. However, the efficacy results differ widely, as the methodology used for studies was very different, as described below.
Conclusion: Stem-cell therapy is promising but still experimental, and further study is needed to identify certain factors. These facts include the ideal type of patient eligible for treatment (apparently those in whom intrinsic urethral dysfunction predominates), and to determine if treatment should be isolated or combined with other cells or procedures, which are the optimal doses and if it is a cost effective procedure.

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Introduction

Urinary incontinence (UI) is a major cause of morbidity in the world and is believed to affect up to 46% of the female population. There are several types of incontinence: urge incontinence or abnormal detrusor activity, stress incontinence (due to inherent sphincter weakness or patients with urethral hypermobility) and mixed incontinence. The most common form of urinary incontinence is stress (SUI), which is currently treated by rehabilitation treatment and surgical techniques, but the effectiveness of these methods is reported to be lower over time. Urge incontinence is often treated which anticholinergic or beta-adrenergic drugs as first line teraphy. Stem-cell therapy for the treatment of stress urinary incontinence is promising but still experimental, and further study is needed to identify certain factors. Our Objective was to analyze the papers that describe stem-cell treatments for women with urinary incontinence to investigate which is the actual Knowledge at this moment specially which are patient population was targeted (which subtype of stress urinary incontinence: only patients with SUI due to inherent sphincter weakness or patients with urethral hypermobility), where is the best site and the best procedure to inject this cells, which is the type of stem cells used and the better dose, and finally what are the results in terms of safety, effectiveness and efficiency.

Material and Methods

We performed a systematic review of the literature from 1946 to date that reports on clinical trials that use stem cells to treat women with urinary incontinence. A systematic review was performed according to PRISMA guidelines using PICO criteria.

Results and Discussion

Nine articles (7 observational and 2 randomized studies) met the inclusion criteria (Table 1). No major adverse effects were observed in any of the studies. However, the efficacy results differ widely, as the methodology used for studies was very different, as described below. All studies were phase II prospective observational studies, except for 2 randomized studies [1,2], in which patients were randomized to different doses of stem cells.

Types of stem cell

In terms of the type of stem cell used, most of the studies used autologous myoblasts collected from biopsies of striated muscle (biceps, pectoral, deltoids, etc.) because muscle cells have the greatest capacity to generate muscle fibers and repair damaged urethral sphincters. Two studies [3, 4] also used autologous fibroblasts for the urethra submucosa, and the study by Lee [5] used stem cells from heterologous umbilical cord. These authors based their approach on a paper by Thornell et al [6], which confirmed that autologous muscle cell efficiency decreases with age.

Inclusion criteria of patients in studies for the treatment of urinary incontinence with stem cells

The inclusion criteria for patients are extremely varied, even within each individual study. All studies excluded urge incontinence or abnormal detrusor activity except for the study by Lee [5], which included 9 patients with mixed UI. However, in SUI, some only required that the patient had stress urinary incontinence (regardless of severity) [2,5,7,8] whereas others include only patients with SUI due to inherent sphincter weakness or at least exclude patients with urethral hypermobility > 45^0 [1,3,9,10]. Nonetheless, it appears that the purpose of stem cells is to regenerate damaged sphincters, rather than to provide urethral support; in fact, some studies exclude patients with prolapse [2,4,9]. In most studies, this treatment was tested in patients who had experienced previous failure of conservative treatment, including electrical stimulation [2,5,7-9]. One study [3] began with rehabilitation treatment, then performed stem-cell injection,

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Reference Year of Publication	Study Design	n	Number of Stem Cells	Injection Site	Outcomes	Follow-up, m
[1] Sebe 2012	Randomized 3 doses	12	Myoblasts Group 1: $1x10^7$ Group 2: $2.5x10^7$ Group 3: $5x10^7$	Sphincter	25%, cures 83%, improvement (dose-independent)	12
[2] Carr 2013	Randomized 2 doses	38	Myoblasts Low dose: $1\text{-}16x10^6$ High dose: $32\text{-}128x10^6$	2 sphincter areas, cystoscope 84% 2 doses	88.9%, improvement high dose 61.5%, improvement, low dose 5.3% worsen	18
[3] Mittelberguer 2007	Prospective interventional + electrical stimulation	123	Myoblasts $2.8x10^7$ Fibroblasts $3.8x10^7$	Rhabdosphincter and submucosa, ultrasound guided	79%, dry 13%, improvement 9%, mild improvement	12
[4] Mittelberguer 2007 2008	Prospective interventional + electrical stimulation	20	Myoblasts $1\text{-}3x10^7$ Fibroblasts $1.4\text{-}6.06x10^7$	Rhabdosphincter and submucosa, ultrasound-guided	89%, dry 11%, improvement	24
[5] Lee 2010	Prospective interventional	39	Umbilical cord $4.3\text{-}1.9x10^8$	Ureterovesical juncture, ultrasound-guided	72.2%, improvement	12
[6] Stangel 2013	Prospective interventional	16	Myoblasts $0.6\text{-}25x10^6$	Rhabdosphincter, cystoscope	50%, dry 25%, improvements 25%, no improvement	24
[7] Carr 2008	Prospective interventional	8	Myoblasts $18\text{-}22x10^6$	Rhabdosphincter, cystoscope (3 patients, reinjection at 3 months)	12.5%, dry 62.5%, improvement	10
[8] Blaganje 2012	Prospective interventional + electrical stimulation	38	Myoblasts $1x10^6\text{-}5x10^7$	Rhabdosphincter, ultrasound-guided (26 injections)	13.5%, cured 78.4%, improvement 8%, equal	1.5
[9] Surcel 2012	Prospective interventional	8	Myoblasts -	Middle urethra, ultrasound-guided	-	12

Table 1: Comparison of the main characteristics of stem cell studies in women with urinary incontinence.

and later performed electrical stimulation for 4 weeks; according to the author this favored stem-cell integration and regeneration. This was also combined with electrical stimulation in the study by Blaganje [9]. Only 1 study [2] considered prior treatment with bulking agents to be an exclusion criterion. A history of anti-incontinence surgery was an exclusion criterion in some studies [9] and an inclusion criterion for others [2]. The series reported by Lee [5] also included 1 patient with a history of surgery. The series studied by Mittelberger [3] was the largest (123 patients), 68 of whom had a history of surgery for incontinence. Naturally, most studies included patients after the physical examination, quality-of-life questionnaires (varied according to author), pad test, urinary diary, urodynamic study, etc., and different criteria were used to select the patients: eg, the pad test threshold was > 5g in 1 hour for Sebe [1] and > 1g in 1 hour for Blaganje [9]. The urodynamic criteria were almost unanimous in requiring normal bladder capacity and absence of obstruction.

Number of stem cell implanted

The stem-cell culture methods also varied considerably according to the author, although even more importantly, there was considerable variation in the number of stem cells to be injected (range, $1x10^6$ to $4.3x10^6 \pm 1.9x10^8$). Some papers stressed research on the ideal number of stem cells; for instance, the randomized studies [1] and [2] compared 2 doses: [1] had 3 arms and found no correlation between the outcomes and the doses used, whereas the other [2] achieved better efficacy in patients who received doses > $32x10^6$. Both also reported that all doses were equally safe. Another study [7] concluded that a small amount of cells ($1x10^6$) was sufficient to achieve continence in some patients.

One of the aspects of concern is whether the local injection of stem cells could have a bulky effect (ie, space-occupying) and, therefore, work for this reason. However, some evidence contradicts these theories. Firstly, there is no correlation showing a stronger effect at higher amounts. Secondly, some articles report that efficacy increases over time after the injection, for instance, Lee reports that 78% improve by 1 month and 80.5% by 3 months. Other studies measured post-injection sphincter electromyographic activity, finding a significant improvement (from 34 to 54 μN), and also measured urethral closure pressure during voluntary contraction (from 0.65 to 1.39) [3,4].

Site and instruments for stem cell injection

Another point of debate is the optimal site and instrument for stem-cell injection. All studies used local anesthesia, most often in the rhabdosphincter [2-4,7-9] under ultrasound or cystoscope guidance. The optimal number of injections is unclear (Blaganje: 2 levels, 26 injections; Surcel: 20 injections in middle urethra; Lee at 4 and 8 o'clock in the vicinity of the urethra and submucosa area; Mittelberguer: myoblast infiltration in the rhabdosphincter and fibroblasts in the submucosa area at 3 levels; Carr 2008, 5 circumferential injections in sphincters; Carr 2013, in 2 areas of the sphincter; Polish studies: at 3 levels).

Several studies (eg, Carr) repeat the dose at 3 months. In [8], patients who had partial improvement and who had improvement at 4 to 8 months but no cure were offered reinjection. In 2013, patients were given an opportunity to receive repeat doses (doses were randomized); 84% chose the procedure and the best outcomes were observed in this

group and were independent of total dose.

Results: safety, effectiveness and efficiency

All studies reported similar safety results. The procedure is safe regardless of the total dose received and showed no noteworthy adverse reactions, even in the study that used heterologous stem cells [5]. The number of participants in each study varied between 8 [10] and 126 [3].

In terms of effectiveness, there are important differences, as to be expected in view of the variability in inclusion criteria described above. The outcomes were measured by physical examination, quality-of-life questionnaires, pad test, urinary diary, transurethral ultrasound , and urodynamic test. Other techniques, such as electromyogram [3,4], were rarely used. Mittelberguer [4] obtained the best medium-term results, specifically a cure (dry) rate of 90% at 1 year of follow-up and 89% at 2 years, with all others improving. This was the only study to inject 2 types of stem cells (myoblasts and fibroblasts) and to use the highest doses (1.4-6.06x107 fibroblasts and 1x107-3x107 myoblasts). Stangel [7] also obtained good outcomes with cure obtained by 50% and partial improvement by 25%). Sebe [1] observed 25% dry patients (83% with improvement), Blaganje [9] 13.5% with cure, 78.4% with improvement, and Carr [8] 12.5% with cure and 62.5% with improvement. All others reported no cure, but did see improvement: Lee [5] reported 72.2% at 1 year, and Carr [2], 88.9% in patients at high doses and 61.5% in patients at low doses at 18 months. Surcel et al. [10] implantated stem cell in the urethral sphincter in four patients with stress urinary incontinence and compared the results of the urodynamic investigations of female patients operated with pure SUI with other surgical techniques. The analyzed procedures were: Burch colposuspension (11 cases), TVT-like (IVS sling in 26 cases), TOT-like (CYSTO-SWING sling in 41 cases). For female patients with myoblasts implant, changes in Q_{max} and P_{ves} at Q_{max} were minimal and statistically insignificant in the context of inclusion criteria, but they noticed a trend of minimal change in these urodynamic characteristics, namely, an average decrease of Qmax with 2.1 mL/s and an average increase of P_{ves} at Q_{max} with 0.6 cm H_2O.

Conclusion

Stem-cell therapy is promising but still experimental, and further study is needed to identify certain factors. These facts include the ideal type of patient eligible for treatment (apparently those in whom intrinsic urethral dysfunction predominates), and to determine if treatment should be isolated or combined (with electrical stimulation), if the treatment should be offered when conservative treatment has failed or when anti-incontinence surgical techniques have failed (the cost difference is significant, being estimated at €1,400 for the tension-free vaginal tape procedure, compared with €5,000 per stem-cell injection [11]). It is also unclear which type of stem cell is best for infiltration, or even whether it should be a single or combined type. Additionally, there is little information on the effective dose or on whether success is dose-dependent. Although the site is the rhabdosphincter, it is also unclear if the treatment should be performed only at this site or also in the submucosa, how many infiltrations should be given, or if they should be repeated after several months. The long-term effectiveness of stem-cell therapy remains to be demonstrated, as the longest study was only 2 years.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

Sanchez- Ferrer ML: conception and design, acquisition of data, analysis and interpretation of data. Involvement in drafting the manuscript or revising it critically for important intellectual contents and final approval of the version to be published.
Machado-Linde F: Conception and design, acquisition of data, Analysis and interpretation of data.
Prieto- Sanchez MT: Conception and design, acquisition of data, Analysis and interpretation of data.
Nieto Diaz A: Final approval of the version to be published.

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