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Original Article

Cell therapy with adipose tissue-derived human stem cells in the urinary bladder improves detrusor contractility and reduces voiding residue

A terapia celular com células-tronco humanas derivadas do tecido adiposo na bexiga urinária melhora a contratilidade do detrusor e reduz o resíduo miccional

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Abstract

Detrusor hypocontractility (DH) is a disease without a gold standard treatment in traditional medicine. Therefore, there is a need to develop innovative therapies. The present report presents the case of a patient with DH who was transplanted with 2 x 10^6 adipose tissue-derived mesenchymal stem cells twice and achieved significant improvements in their quality of life. The results showed that cell therapy reduced the voiding residue from 1,800 mL to 800 mL, the maximum cystometric capacity from 800 to 550 mL, and bladder compliance from 77 to 36.6 mL/cmH_2O. Cell therapy also increased the maximum flow from 3 to 11 mL/s, the detrusor pressure from 08 to 35 cmH_2O, the urine volume from 267 to 524 mL and the bladder contractility index (BCI) value from 23 to 90. The International Continence on Incontinence Questionnaire – Short Form score decreased from 17 to 8. Given the above, it is inferred that the transplantation of adipose tissue-derived mesenchymal stem cells is an innovative and efficient therapeutic strategy for DH treatment and improves the quality of life of patients affected by this disease.

Keywords: adipose derived mesenchymal stem cells, cellular therapy, urinary bladder, urodynamics, lower urinary tract.

Resumo

A Hipocontratilidade Detrusora (HD) é uma doença sem um tratamento padrão-ouro na medicina tradicional. Logo, há a necessidade de desenvolvimento de terapias inovadoras. O presente relato apresenta um caso de paciente com HD transplantado duas vezes com 2 x 10^6 células-tronco mesenquimais derivadas do tecido adiposo que obteve melhoras significativas em sua qualidade de vida. Os resultados demonstraram que a terapia celular reduziu o resíduo miccional de 1.800mL para 800mL; a Capacidade Cistométrica Máxima de 800 para 550mL; a complacência de 77 para 36,6mL/cmH_2O. A terapia celular também aumentou o fluxo máximo de 3 para 11mL/s; a pressão detrusora de 08 para 35cmH_2O; o volume urinado de 267 para 524mL e o índice de contratilidade vesical (BCI) de 23 para 90. O score do International Continence on Incontinence Questionare – Short Form passou de 17 para 8. Diante do exposto, infere-se que o transplante de células-tronco mesenquimais derivadas do tecido adiposo é uma estratégia terapêutica inovadora e eficiente para o tratamento da HD e para melhoria da qualidade de vida de pacientes acometidos por essa doença.

Palavras-chave: células-tronco mesenquimais derivadas de tecido adiposo, terapia celular, bexiga urinária, urodinâmica, trato urinário inferior.

1. Introduction

Detrusor hypocontractility (DH) is related to short-duration contraction of the detrusor, which results in low pressure associated with low urinary flow (D'ancona et al., 2019). Patients affected by this disease experience a slow urinary flow, hesitation and an increased effort to urinate, a feeling of incomplete bladder emptying and high postvoiding residue (Gammie et al., 2016).

According to Levanovich et al. (2015), muscle-derived cells are able to reduce cystometric capacity and restore the ability to urinate in small volumes. Even with these

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improvements, patients with DH remain dependent on catheterization. This was the only cell therapy report found in the researched literature for the treatment of DH. However, there are studies in urology with cell therapy and tissue engineering for the repair of renal, gonadal, urethral sphincter and bladder tissues (Becker and Jakse, 2007; Levanovich et al., 2015; Assis et al., 2019; Oliveira et al., 2019). These facts demonstrate the need to continue studies in this area.

The fact that conventional therapies do not present the desired gold standard reinforces the need for studies of DH treatment. Given the above, in the present study, the effects of cell therapy with adipose tissue-derived human mesenchymal stem cells in the treatment of DH are reported.

2. Case History

A 74-year-old white male patient with a history of a weak and intermittent urinary stream, very prolonged urination, hesitation, a feeling of incomplete emptying, pain and bulging in the hypogastrium was referred to the Urology Service of Hospital Universitário Maria Aparecida Pedrossian (HUMAP), a public hospital of Sistema Único de Saúde (SUS), Campo Grande, MS, Brazil. The previous history showed recurrent urinary infection and the use of a Foley urinary catheter due to urinary retention for one year. The patient had no history of smoking, alcoholism and comorbidities except hypertension. The patient was taking losartan (50 mg/day).

On physical examination, he had normal external genitalia, a bulging abdomen and pain in the hypogastric region. Digital rectal examination revealed a prostate < 30 grams, nodules and painlessness. Blood count and coagulogram results were normal. Ultrasonography showed normal kidneys, a bladder with an accentuated voiding residue and a 20-gram prostate.

Urethrocystoscopy showed a normal penile, bulbar and membranous urethra; a normal prostatic urethra; an open bladder neck; a topical ureteral meatus; and smooth bladder walls without trabeculations.

3. Results

The patient underwent a urodynamic study to assess voiding dysfunction. The initial uroflowmetry test did not trigger urination and showed a voiding residue of 1,800 mL measured by urinary catheter. Differential cystometry showed a maximum cystometric capacity (MCC) of 800 mL, a bladder compliance of 77 mL/cmH_2O, decreased sensitivity, losses with effort manoeuvres and the absence of contractions. The flow-pressure study presented a maximum flow (Qmax) of 3 mL/s, a detrusor pressure at maximum flow (pdetqmax) of 8 cmH_2O, a urine volume of 267 mL, and a detrusor contractility index (bladder contractility index: BCI = pdetqmax + 5 x Qmax) of 23. The values obtained with this urodynamic study were compatible with DH (Table 1).

Table 1. Absolute values and percentage of variation in the results of uroflowmetry, cystometry and flow pressure study and score of the International Continence on Incontinence Questionare – Short From, before and after cell therapy.

Uroflowmetry			
	Before	**After**	**%**
Maximum Flow	0	10	1000
Medium flow	0	5	500
Volume urinated	0	176	17600
Residue	1800	800	-56
Cystometry			
	Before	**After**	**%**
CCM	800	550	-31
Urinary Loss	Yes	No	
Hyperactivity	No	No	
Complacency	77	33.6	-52
Pressure Flow Study			
	Before	**After**	**%**
Maximum Flow	3	11	267
Maximum Detrusion Pressure	8	35	338
Volume urinated	267	524	96
BCI	23	90	291
International Continence on Incontinenca Questionaire			
	Before	**After**	**%**
ICIQ-SF	17	8	-53%

Caption: CCM - Maximum cystometric capacity; BCI - Vesical Contractility Index.

The ICIQ-SF (International Continence on Incontinence Questionnaire – Short Form) was applied to assess quality of life, with the patient obtaining a score of 17 (Table 1).

The standard treatment for cases of DH was started with clean intermittent catheterization and clinical and laboratory follow-up. The maximum volume in each drain was 400 mL. In the present condition, the patient needed 5 catheters/day. Given the above, the patient was recruited for treatment with mesenchymal stem cells (Opinion confirmed by CEP/CONEP number #2,745746).

After agreement and signing the informed consent form, the patient underwent liposuction for peripheral fat collection from the inner face of the right and left thigh. The procedure was performed by a specialist in plastic surgery on an outpatient basis. A total of 125 mL of anaesthetic solution containing 20% lidocaine without adrenaline, 0.9% saline and 8.4% sodium bicarbonate was used. A total of 200 ml of phosphate buffer solution (PBS) was removed. Then, the material was sent to the Center for Studies in Stem Cells, Cell Therapy and Toxicological Genetics (CeTroGen) and processed according to a current standard operating procedure established by Pesarini et al. (2018).

At 60 days, the patient underwent outpatient urethrocystoscopy for transplantation of 2 x 10^6 adipose

tissue-derived mesenchymal stem cells. The transplant was performed at 5 points in the body of the bladder above the vesical triangle. A second transplant was performed 30 days after the first following the same principles.

The patient was clinically followed up during and after the transplant and submitted to a cultured urine test. The patient did not present any complications, and the exams showed normal results.

At 60 days after transplantation, the patient underwent a new urodynamic study. The initial uroflowmetry test showed a maximum flow of 10 mL/s, an average flow of 5 mL/s, a urine volume of 176 mL and a residual volume of 800 mL. Differential cystometry showed a maximum cystometric capacity of 550 mL, a bladder compliance of 36.6 mL/cmH_2O, decreased sensitivity with no loss and involuntary detrusor contraction. The pressure-flow study showed a maximum flow of 11 mL/s and pdetQmax of 35 cmH_2O. The urine volume was 524 mL, and the BCI value reached 90 (Table 1).

When administered the ICIQ-SF, the patient received a score of 8 (Table 1).

4. Discussion

The patient was unable to trigger urination. Therefore, the only way to empty the bladder was through clean intermittent catheterization. In the first uroflowmetry test, the patient had a voiding residue of 1800 mL. This volume suggests a diagnosis of detrusor contractility. Detrusor contractility is diagnosed for patients with voiding residues greater than 1,000 mL (Anderson and Grant, 1991). However, it was observed that this patient had a detrusor pressure of 8 cm/H_2O. Therefore, the suggested diagnosis was DH.

The diagnosis of DH was confirmed (I) by the low maximum flow of only 3 mL/s, while the expected one was above 15 mL/s (Reynard et al., 1998); (II) due to the small detrusor pressure, which was only 8 cmH_2O, while the expected one was 30 cmH_2O (Zerati et al., 2010); and (III) because of the low BCI value, which was only 23, while the expected range was between 100 and 150 (D'ancona et al., 2019).

This condition interfered with the quality of life of the patient, who obtained a score of 17 on the ICIQ-SF, which has a maximum score of 21 (Tamanini et al., 2004). Patients with DH reduce or withdraw from their daily activities, especially from social interactions, as clean intermittent catheterization is difficult to perform outside the home. In addition, this disease leads to urine loss, which is perceived by the unpleasant smell and causes social embarrassment (Teunissen et al., 2006).

Given the above, it is believed that conventional therapy, which involves clean intermittent catheterization and the surveillance of renal function and urinary tract infections (Bayrak and Dmochowski, 2019), leads to improvements for these patients. However, the results are not satisfactory. Therefore, there is a need for innovative therapies that can improve the quality of life of patients with results beyond those obtained with conservative treatments. In this context, cell therapies using mesenchymal stem cells stand out.

In the present study, two transplants with adipose tissue-derived mesenchymal stem cells were able to confer the ability to trigger urination. In addition, the uroflowmetry test showed an improvement of 1000%, 500% and 17600% in maximum flow, mean flow and urine volume, respectively. The improvement of these parameters resulted in a 56% lower voiding residue. It was also observed that the CCM reached a value of 550 mL, and the expected value was between 350 and 500 mL, which demonstrated a reduction of 31%. Initially, the patient had urinary loss, and after therapy, the cells stopped. Bladder compliance showed a reduction of 52%, decreasing from 77 mL/cmH_2O to 36.6 mL/cmH_2O, with the expected values being above 30 mL/cmH_2O (D'ancona et al., 2019).

The pressure flow study demonstrated a maximum flow increase of 267%. This parameter increased from 3 to 11 mL/s, and the expected range was above 15 mL/s (Ahmed et al., 2016). The urine volume increased by 96%. However, the voiding residue remains high according to D'Ancona et al. (2019), who report this should be up to 50 mL. The BCI value showed an increase of 291%, reaching a value of 90, with the expected value being between 100 and 150 (D'ancona et al., 2019).

All these improvements were directly reflected in the quality of life of the patient who presented an ICIQ-SF score of 8 after cell therapy. Thus, there was a 53% reduction in the score, which directly reflected the patient's daily life and the resumption of their daily activities and social interaction. It is also noteworthy that this patient's intermittent catheterizations decreased from 5 to 2 per day, and he acquired spontaneous urination. Given the above, we infer that the transplantation of adipose tissue-derived mesenchymal stem cells is an innovative therapeutic strategy for the treatment of DH and for improving the quality of life of patients affected by this disease.

Mesenchymal stem cells, especially those derived from adipose tissue, have been successfully used clinically (Bacakova et al., 2018). Their applications in skin rejuvenation and wound healing (Hanson et al., 2010; Tobita et al., 2011; Nae et al., 2013; Kokai et al., 2014), in Parry-Romberg syndrome treatment (Sterodimas et al., 2010), inflammatory and/or autoimmune disorders such as Graft versus host disease, multiple sclerosis and Crohn's disease (Locke et al., 2009; Frolich et al., 2014; Kokai et al., 2014; Wainstein et al., 2018; Bernardi, et al., 2022), in bone repair (maxilla, calvaria -severe head injury) (Kokai et al., 2014), in osteoarthritis (Schweich-Adami, et al., 2021; Schweich-Adami, et al., 2022a, 2022b), in critical ischemia (Lee et al., 2012; Bura et al., 2014), in post-traumatic brachial plexus injury (Thakkar et al., 2014) and in paraplegia after traumatic spinal cord injury (Thakkar et al., 2016), have been described. However, there are no relevant reports on the use of adipose tissue-derived mesenchymal stem cells in renal and/or urological diseases. This fact reinforce the pioneering spirit of this study and our results confirm the therapeutic potential of this cell in the treatment of detrusor hypocontractility, a urological disease that is difficult to manage and treat. This is the first report of cell

therapy using adipose tissue-derived mesenchymal stem cells for the treatment of DH in the SUS.

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