Clinical case

Intracavernous application of autologous bone marrow stem cells for medical treatment-refractory erectile dysfunction: A case report

Aplicación intracavernosa de células madre autólogas de médula ósea para el manejo de disfunción eréctil refractaria: Experiencia de un caso

José Iván Robles-Torres,[1] Consuelo Mancías-Guerra,[1] Alejandra Garza-Bedolla,[1] Lauro Salvador Gómez-Guerra.[1*]

Abstract

Clinical case description: A 61-year-old man with severe erectile dysfunction related to diabetes mellitus of long duration was treated through intracavernous stem cell application. Transplantation of autologous bone marrow stem cells through a single intracavernous injection was performed. Clinical response, Doppler ultrasound of the penis, and adverse events were evaluated during the 50-week follow-up. The highest clinical response was reported at week 12, but it diminished thereafter. At the end of follow-up, ultrasound identified the presence of neovascularization emerging from the cavernous arteries.

Relevance: Numerous preclinical trials have demonstrated efficacy and safety, but there is insufficient clinical evidence showing promising results.

Clinical implications: No adverse events were detected, and ultrasound revealed hemodynamic changes that were possibly related to the therapy. The source and dosage of stem cells, as well as subsequent therapeutic applications, pose questions that remain to be answered.

Conclusions: Stem cell therapy for erectile dysfunction is a field of research that has sparked interest in numerous scientific groups, but clinical experience is still limited.

Keywords:
Cell therapy, Erectile dysfunction, Stem cells.

Corresponding:
*Lauro Salvador Gómez-Guerra. Av. Francisco I. Madero Pte. S/N and Av. Gonzalitos, Mitras Centro 64460, Monterrey, Mexico. Email: laurogomez@hotmail.com

Citación: Robles-Torres J.I., Mancías-Guerra C., Garza-Bedolla A., Gómez-Guerra L.S. *Intracavernous application of autologous bone marrow stem cells for medical treatment-refractory erectile dysfunction: A case report*. Rev Mex Urol. 2020;80(2):pp 1-9

[1] Universidad Autónoma de Nuevo León, Hospital Universitario "Dr. José Eleuterio González", Monterrey, Nuevo León, México.

Recepción: September 23, 2019
Aceptación: March 24, 2020

Resumen

Descripción del caso clínico: Presentamos un masculino de 61 años con disfunción eréctil severa relacionada a diabetes mellitus de larga evolución manejado con células madre intracavernosas. Se realizó trasplante autólogo de células madre obtenidas de médula ósea en dosis única aplicadas vía intracavernosa. Se realizó un seguimiento de 50 semanas que evaluó la respuesta clínica, la ecografía doppler del pene y los eventos adversos. La respuesta clínica más alta se reportó en la semana 12, pero posteriormente disminuyó. Los hallazgos ecográficos revelaron la presencia de neovascularización que emerge de las arterias cavernosas al final del seguimiento.

Relevancia: Numerosos estudios preclínicos han demostrado eficacia y seguridad. Se ha reportado evidencia clínica limitada que muestra resultados prometedores.

Implicaciones clínicas: No se detectaron eventos adversos y la ecografía mostró cambios hemodinámicos, posiblemente relacionados con la terapia. Las aplicaciones posteriores, la fuente de células madre y la dosis siguen siendo preguntas sin responder.

Conclusiones: La terapia con células madre para la disfunción eréctil es un campo que ha despertado el interés de numerosos grupos científicos. Sin embargo, la experiencia clínica sigue siendo limitada.

Palabras clave: terapia celular, disfunción eréctil, células madre.

Introduction

Erectile dysfunction (ED) is a condition of considerable prevalence worldwide, affecting 19.2% of the male population.[1] Currently, first-line treatment for ED consists of phosphodiesterase type 5 (PDE-5) inhibitor use and changes in lifestyle. Intracavernous injection of prostaglandin analogs and penile prosthesis are other available treatment modalities used in cases of severe erectile dysfunction that do not respond to first-line treatment.[2]

The inconvenience of those therapeutic modalities lies in the high risk of adverse events, such as local pain and bruising related to continuous prostaglandin analog injections, infections, and complications related to the surgical procedure of penile prosthesis. Stem cell (SC) therapy appears to be a promising option in that group of patients.[3,4]

We present our experience of a patient with medical treatment-refractory ED, who rejected second and third-line therapy, and instead, opted for transfusion with autologous bone marrow total nucleated cells at our hospital.

Clinical case

A 61-year-old man sought medical attention at the Urology Department, complaining of a

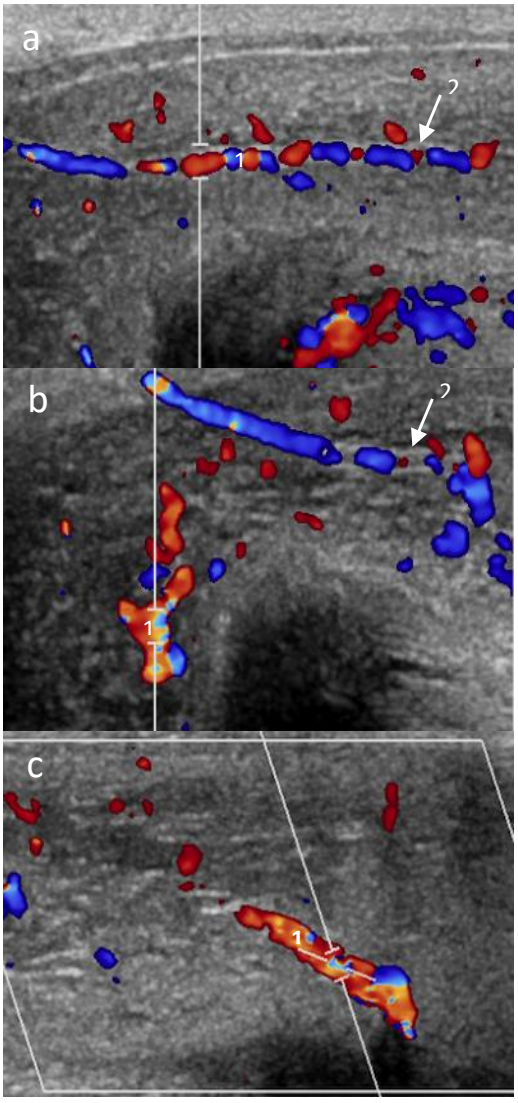
12-month history of not being able to keep an erection firm, resulting in the inability to have sexual intercourse. He took multiple PDE-5 inhibitors regularly for 8 months, with no improvement, and underwent the application of intracavernous prostaglandins for 3 months, with poor response. The patient had a medical history of diabetes mellitus diagnosed at 36 years of age, poor treatment adherence, and was receiving insulin for the first time for the past 6 months. He also had a long personal history of smoking and occasional drinking.

The patient's body mass index (BMI) was 27.7 kg/m2. He stated that he did not have nocturnal erections and that he was unable to achieve firm erections through sexual stimulation, despite having sexual desire. The patient answered the 5-item version of the International Index of Erectile Function (IIEF-5) questionnaire. His score was 6, indicating severe ED. Physical examination revealed no significant abnormalities.

Laboratory work-up reported a complete blood count (CBC) within normal parameters, creatinine of 1.4mg/dL, fasting glucose of 150 mg/dL, and glycosylated hemoglobin of 8.2%. Total testosterone was 552 ng/dL (normal range of 240-950 ng/dL) and free testosterone was 8.1ng/dL (normal range of 3.67-13.9 ng/dL).[5] Infectious diseases (human immunodeficiency virus, hepatitis B, hepatitis C, and syphilis) were ruled out by standard methods.

A penile color Doppler ultrasound (CDUS) was performed, using alprostadil 10 mcg (Caverject®). Results showed hyperechoic images following the vascular tract, suggestive of atheromatous plaque in both cavernous arteries, with a diameter of 0.09mm (Figure 1). The registered peak systolic velocity (PSV) was 6.3cm/s before alprostadil injection, and 17.5cm/s 20 minutes after injection (PSV-20). Together with the patient's medical background, the imaging study findings confirmed severe erectile dysfunction of vascular etiology.

Figure 1. Color Doppler ultrasound of the penis at week 0



a) Right cavernous artery (RCA)1 pre-injection, with atheromatous plaque2, PSV= 4.61cm/s; b) RCA1 10 min post-injection, atheromatous plaque2 observed, PSV= 17.0cm/s; c) RCA1 20 min post-injection, PSV= 17.5cm/s. Irregular blood flow shown in a), b), and c).

Penile implant was proposed but the patient rejected the procedure due to its surgical risks and high cost.

Intervention protocol

The intervention was approved by the local bioethics committee of our hospital (EH-230-16) and the patient's statement of informed consent was signed after a detailed explanation about the procedure and possible adverse effects. To undergo the intervention, the patient had to meet the following criteria: ≥ 18 years of age, a history of type 2 diabetes mellitus >10 years, IIEF-5 score <8 (severe ED), and a history of chronic ED for at least 6 months that was unresponsive to PDE-5 inhibitors, used regularly for at least 3 months. The exclusion criteria were: anatomic deformities of the penis, a history of priapism, neoplasm, hypogonadism, low serum testosterone (<200 ng/dL), or any anticoagulant therapy.

The patient was asked to discontinue treatment with the PDE-5 inhibitor two weeks before the protocol. Prior to bone marrow harvesting, autologous bone marrow (BM) stimulation was carried out subcutaneously with 10 ug/kg of granulocyte colony-stimulating factor (G-CSF), for 3 days. Another CBC was performed to determine the increase of cell concentration in peripheral blood. BM harvesting was performed under sedation and local anesthesia. In the prone position, and after asepsis, Jamshidi needles were inserted in both posterior iliac crests to aspirate a total volume of 200 ml. The sample was collected in 4 sterile 50-ml Corning tubes, after the addition of an anticoagulant solution.

The sample contained in the Corning tubes was filtered in a laminar flow cabinet, using a 180-um blood filter, centrifuged at 2600g for 15 minutes at 6ºC, and then returned to the flow cabinet, as the first part of the isolation method to obtain the buffy coat. Plasma was removed with a 16-gauge needle 2 mm above the buffy coat and discarded. Using the same syringe, the buffy coat was obtained manually at a volume of approximately 2 ml for each Corning tube. Red blood cells were excluded. The isolated buffy coat was recovered in a single sterile 10-mL syringe and diluted with saline solution to obtain an approximated final volume of 8 ml for intracavernous administration. After homogenizing, a 0.5-mL sample of the buffy coat was used to perform a CBC, bacterial cultures, and flow cytometry, to enumerate CD34+ cells, CD45+ cells, and viability assessment using anti-CD34 and anti-CD45 antibodies and 7-aminoactinomycin D, respectively. Cellular components and sample concentration are described in Table 1.

Table 1. Cellular components and concentration of the sample

2.1 million total CD34+
350.3 CD34/µL
4,444 x 10^6 Total Cells
Viability of 94.1%

After asepsis and local anesthesia, 4 mL of the sample was injected at the external surface of each cavernous body in the proximal third of

the flaccid penis. The penile root was clamped for 2 minutes. No complications were reported. The entire procedure was performed, and the patient was discharged, both on the same day.

Follow-up Assessment

The current treatment for ED, adverse effects, the Erection Hardness Score (EHS), and the IIEF-5 were evaluated at each follow-up appointment, scheduled at weeks 4, 8, 12, 16, 20, 32, and 50 (Figure 2). CDUS was performed prior to SC transplantation (baseline) at week 12 and week 50 (Figure 3). Detailed data obtained in the imaging studies are shown in Table 2.

Figure 2. Follow-up of the Erection Hardness Score (EHS) and the 5-item version of the International Index of Erectile Function (IIEF-5)

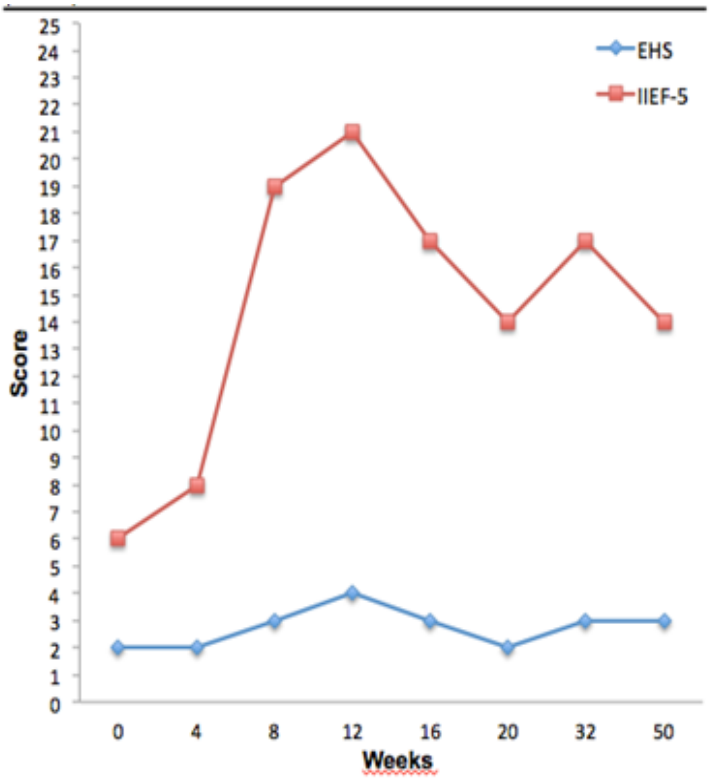
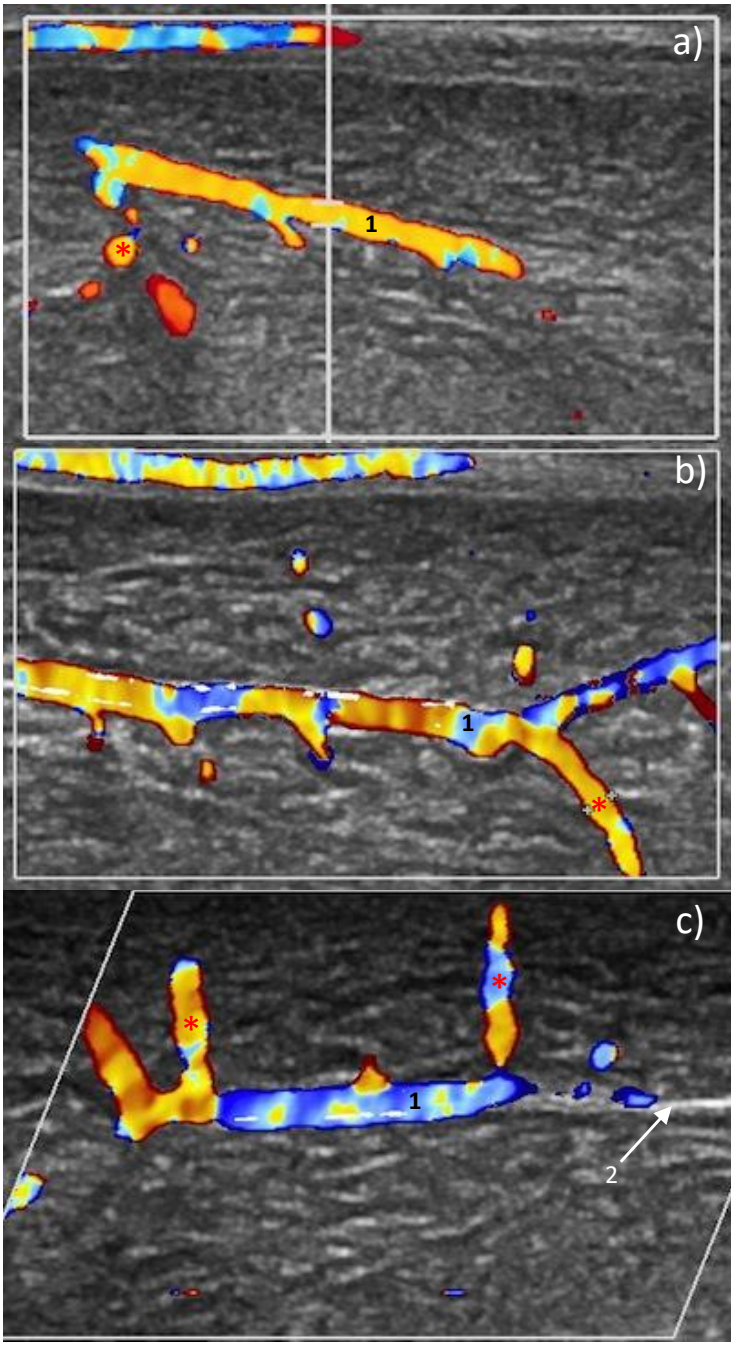


Figure 3. Color Doppler ultrasound of the penis at week 50



a) Right cavernous artery (RCA)1 pre-injection, showing regular blood flow, PSV= 10.0cm/s; b) RCA1 10 min post-injection, PSV= 18.2cm/s; c) RCA1 20 min post-injection, and atheromatous plaque2, PSV= 30.0cm/s. Helicine arteries (asterisk) are observed in a), b), and c).

Table 2. Color Doppler ultrasound of the penis, follow-up at baseline (week 0), week 16, and week 50

	Baseline (Week 0)	*Week 16*	*Week 50*
PSV*	6.3cm/s	7cm/s	9.7cm/s
PSV-10*	17.5cm/s	12.5cm/s	19cm/s
PSV-20*	23.5cm/s	20cm/s	29.5cm/s
EDV*	0cm/s	0cm/s	0cm/s
EDV-10*	4.25cm/s	3.10cm/s	3.5cm/s
EDV-20*	5cm/s	4.5cm/s	7.05cm/s
Diameter of cavernous artery*	0.094cm	0.063cm	0.097cm
Diameter of cavernous artery-20*	0.098cm	0.098cm	0.10cm/s
Additional findings	Atheromatous plaques in cavernous arteries, irregular blood flow	Atheromatous plaques in cavernous arteries, irregular blood flow	Helicine arteries are visible, regular blood flow in cavernous arteries

PSV = Peak Systolic Velocity; PSV-10 = Peak Systolic Velocity 10 minutes post-prostaglandin injection; PSV-20 = Peak Systolic Velocity 20 minutes post-injection; EDV = End-Diastolic Velocity; EDV-10 = End-Diastolic Velocity 10 minutes post-injection; EDV-20 = End-Diastolic Velocity 20 minutes post-injection; *All parameters are the mean values of the left and right cavernous arteries.

Results

Compared to the baseline CDUS, at week 50, a higher PSV and PSV-20 was registered. However, there were no differences in the diameters of the cavernous arteries and no atheromatous plaque. An additional finding was the presence of prominent collateral vessels, consistent with helicine arteries, with regular blood flow and high PSV. Those findings were not registered in previous studies.

During follow-up, treatment with PDE-5 inhibitors was discontinued. Nocturnal erections were reported at week 8, and the ability to perform sexual intercourse was achieved at week 10. Satisfactory sexual intercourse lasted 10 minutes, with a frequency of 3 episodes per week.

The highest scores during follow-up were at week 12, with an IIEF-5 score of 21 pts and an EHS of 4, classified as mild erectile dysfunction that was responsive to PDE-5 inhibitors. After week 12, the quality of the erections gradually declined. However, good response to PDE-5 inhibitors persisted over time.

Discussion

We detected a peak response to therapy at week 12 of follow-up, similar to the findings published by Bahk et al. (2010) and Yiou et al. (2016), who reported a maximum response between weeks 4 and 12.[6,7] However, there was a lack of correlation between the clinical features (measured by IIEF-5 and EHS) and the imaging

studies (CDUS results). CDUS results showed constant improvement at the end of follow-up, whereas IIEF-5 and EHS scores showed temporary improvement with a progressive decline up to the end of follow-up.

Levy et al. published a study on 8 men with organic causes of ED, using placenta-derived SCs. Results were not very encouraging, resulting in improved erection in 3 of the 8 patients and no significant change in the IIEF-5. CDUS of the penis showed no significant hemodynamic changes.[8] Haahr et al. studied the use of adipose-derived mesenchymal SCs in 17 patients after radical prostatectomy. Eight of the 17 patients recovered erection and had significant improvement on the IIEF-5 questionnaire.[9] Al Demour S et al. reported a similar intervention in patients with ED and diabetes mellitus. Four diabetic patients with refractory ED were included. Two consecutive intracavernous autologous BM mesenchymal SCs injections were performed. A significant improvement on the IIEF-15 and EHS scores were reported and no significant adverse effects were found.[10]

The presence of prominent helicine arteries with a high PSV was an outcome not described in previous clinical trials. However, those findings were reported in several preclinical trials performed on rat models.[6-9] Those multiple tortuous vessels branch off at the cavernous artery and open directly into the cavernous spaces, acting as resistance arteries. The importance of those vascular structures is in the mechanism of penile resistance of the arterial smooth muscle. They act as sphincters and regulate blood flow between the systemic circulation and the cavernous sinusoids, an essential phenomenon for erectile function.[11]

The role of SCs in the management of ED is limited. Based on evidence that SCs are able to differentiate into several cell types, including endothelial cells (ECs), smooth muscle cells (SMCs), neurons, and other cell types involved in the pathophysiology of ED, their application for the condition appears promising. Recent studies have guided their research, based on that knowledge of SCs, to regenerate dysfunctional ECs, cavernous nerves, and cavernous SMCs.[12]

No conclusions can be made due to the limitations of the present study, but it paves the way for future clinical trials on SC therapy for ED that aim to determine the safety, efficacy, and ideal source and concentration of SCs and subsequent applications, as well as to provide answers to other questions that remain. Even though there are many studies and the results of SC therapy are encouraging, there is still insufficient evidence and inadequate protocol standardization.

References

1. **Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U.** Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. Int J Impot Res. 2000 Dec;12(6):305–11. doi: http://dx.doi.org/10.1038/sj.ijir.3900622
2. **Soebadi MA, Moris L, Castiglione F, Weyne E, Albersen M.** Advances in stem cell research for the treatment of male sexual dysfunctions: Current Opinion in Urology. 2016 Mar;26(2):129–39. doi: http://dx.doi.org/10.1097/mou.0000000000000255
3. **Reed-Maldonado AB, Lue TF.** The Current Status of Stem-Cell Therapy in Erectile Dysfunction: A Review. World J Mens Health. 2016;34(3):155. doi: http://dx.doi.org/10.5534/wjmh.2016.34.3.155

4. **Alwaal A, Hussein AA, Lin C-S, Lue TF.** Prospects of stem cell treatment in benign urological diseases. Korean J Urol. 2015;56(4):257. doi: http://dx.doi.org/10.4111/kju.2015.56.4.257
5. **Mayo Medical Laboratories.** TTFB - Clinical: Testosterone, Total, Bioavailable, and Free, Serum. 2016. [accessed 2 Apr 2020] Available from: https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/83686
6. **Bahk JY, Jung JH, Han H, Min SK, Lee YS.** Treatment of diabetic impotence with umbilical cord blood stem cell intracavernosal transplant: preliminary report of 7 cases. Exp Clin Transplant. 2010;8(2):150–60.
7. **Yiou R, Hamidou L, Birebent B, Bitari D, Lecorvoisier P, Contremoulins I, et al.** Safety of Intracavernous Bone Marrow-Mononuclear Cells for Postradical Prostatectomy Erectile Dysfunction: An Open Dose-Escalation Pilot Study. European Urology. 2016 Jun;69(6):988–91. doi: http://dx.doi.org/10.1016/j.eururo.2015.09.026
8. **Levy JA, Marchand M, Iorio L, Cassini W, Zahalsky MP.** Determining the Feasibility of Managing Erectile Dysfunction in Humans With Placental-Derived Stem Cells. J Am Osteopath Assoc. 2016 Jan 1;116(1):e1. doi: http://dx.doi.org/10.7556/jaoa.2016.007
9. **Haahr MK, Jensen CH, Toyserkani NM, Andersen DC, Damkier P, Sørensen JA, et al.** Safety and Potential Effect of a Single Intracavernous Injection of Autologous Adipose-Derived Regenerative Cells in Patients with Erectile Dysfunction Following Radical Prostatectomy: An Open-Label Phase I Clinical Trial. EBioMedicine. 2016 Mar 1;5:204–10. doi: https://doi.org/10.1016/j.ebiom.2016.01.024
10. **Al Demour S, Jafar H, Adwan S, AlSharif A, Alhawari H, Alrabadi A, et al.** Safety and Potential Therapeutic Effect of Two Intracavernous Autologous Bone Marrow Derived Mesenchymal Stem Cells injections in Diabetic Patients with Erectile Dysfunction: An Open Label Phase I Clinical Trial. Urol Int. 2018;101(3):358–65. doi: http://dx.doi.org/10.1159/000492120
11. **Prieto D. Physiological regulation of penile arteries and veins. Int J Impot Res.** 2008 Jan;20(1):17–29. doi: http://dx.doi.org/10.1038/sj.ijir.3901581
12. **Gómez-Guerra LS, Robles-Torres JI, Garza-Bedolla A, Mancías-Guerra C.** Erectile dysfunction treated with intracavernous stem cells: A promising new therapy? Revista Internacional de Andrología. 2018 Jul;16(3):119–27. doi: http://dx.doi.org/10.1016/j.androl.2017.10.003