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REVIEW

Erectile dysfunction treated with intracavernous stem cells: A promising new therapy?

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Abstract In the past decades, great interest has been shown in the development of new therapies for erectile dysfunction. Stem cell therapy has generated promising results in numerous preclinical trials in animal models, which is why has led to the development of the first clinical trials in humans. The main cause involved in the pathophysiology of erectile dysfunction is vascular damage related to endothelial and neuronal injury. The interest in stem cell therapy is justified by their capability to differentiate into specific damaged tissues, including endothelium and nervous tissue, and induction of the host own cell proliferation. Despite the great effort of the many studies carried out to date, knowledge about biological effects, therapeutic efficacy and safety of stem cells therapy for erectile dysfunction is still very limited.

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PALABRAS CLAVE

Disfunción eréctil;
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Intracavernoso

Células madre vía intracavernosa para el tratamiento de la disfunción eréctil: ¿una nueva modalidad terapéutica?

Resumen En las últimas décadas, ha habido gran interés en el desarrollo de nuevos tratamientos para tratar la disfunción eréctil. El tratamiento con células madre ha arrojado prometedores resultados en numerosos estudios preclínicos en modelos animales, lo cual ha generado el desarrollo de los primeros ensayos clínicos en seres humanos. Puesto que la principal causa implicada en la fisiopatología de la disfunción eréctil es una lesión vascular asociada con lesión endotelial y neuronal, el interés por el tratamiento con células madre se justifica por la capacidad que tienen para diferenciarse en los distintos tejidos dañados, incluyendo endotelio y tejido neuronal, y en la inducción de la reparación de las propias células del huésped. A pesar del gran

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esfuerzo de los distintos estudios realizados hasta el momento actual, el conocimiento sobre los efectos biológicos, la eficacia terapéutica y la seguridad del tratamiento con células madre aún se encuentra muy limitado.

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Introduction

Erectile dysfunction (ED) is defined as the inability to attain or maintain a penile erection satisfactory for sexual intercourse.¹ The incidence of ED has been increasing in the past decades, affecting 19.2% of male global population. There is a clear association with age, affecting from 2.3 to 53.4% of men aged 30 to 80 years, respectively.²

Risk factors for ED are similar to those associated with cardiovascular disease, including hypertension, hyperlipidemia, diabetes, smoking, and obesity. The main components in the physiology of erection are the endothelial cells (EC), the cavernous smooth muscle cells (CSMC), and the neuronal nitric oxide (NO) synthase-positive cavernous nerves.³ The high prevalence of ED in patients with cardiovascular diseases, along with the fact that endothelial dysfunction and reduced availability of NO often underlie vascular diseases, suggests the essential role of the EC in the pathogenesis of ED.⁴

The present work is a review of the available information and evidence of stem cell (SC) therapy in clinical trials published and those that are currently under development.

Pathophysiology of erectile dysfunction of vascular etiology

The main cause of erectile dysfunction is of vascular etiology. Patients with Diabetes Mellitus (DM) type 1 and 2 exhibit impaired new blood vessel development in response to ischemia, so they are prone to present vascular complications leading to end organ damage, including ED. The hallmark of these vascular complications is endothelial dysfunction, causing cellular apoptosis.⁵

In hyperlipidemia, atherosclerosis of cavernous vessels is a common event, but it is also associated with the decreased levels of cavernous NO, and the subsequent impairment of cavernous nerves and EC function.⁶

Currently, the first line treatment for ED is 5-phosphodiesterase inhibitors (5-PDEI). These drugs are competitive and reversible inhibitors of cyclic guanosine monophosphate (cGMP) hydrolysis. The clinical effect is a potentiation of NO function, caused by intracellular accumulation of cGMP, which reduces cytosolic levels of calcium inside CSMC. The final result is an increased relaxation of smooth muscle and blood accumulation into the corpus cavernosum by an increased arterial inflow and a decreased venous outflow (Fig. 1).⁷

In order to obtain the therapeutic effect of 5-PDEI, neuronal nitric oxide synthase (nNOS)-positive cavernous nerves and EC function must be partially or completely preserved, in order to produce the sufficient blood concentrations of NO to activate guanylyl cyclase and produce cGMP inside CSMC.⁸ For this reason, diseases such as DM, hyperlipidemia and radical prostatectomy, in which cavernous nerves and EC are severely damaged, the efficacy of 5-PDEI is limited and usually unsatisfactory (Fig. 2).⁹

Except for lifestyle changes and penile revascularization, the outcome of the available treatments is not the expected due to the subjacent cause of the disease. In other words, conventional therapies do not intervene in the recovery of nerve and endothelial tissue function, being the role of the drugs described above only a palliative measure.¹⁰

Therefore, invasive therapies, such as intracavernous injection of prostaglandin analogs, and surgical procedures, such as the penile prosthesis implantation, are considered to be of choice in ED related to these diseases. The inconvenience of these therapeutic modalities lies in the high risk of adverse events, such as local pain and bruising related to prostaglandin analogs injection, and infections and complications related to the surgical procedure in penile prosthesis.^{11,12} In these group of patients stem SC therapy seems to be a promising treatment.¹³

Penile revascularization deserves a special consideration. This therapeutic option consists of surgical anastomosis, similar to cardiac bypass, between the epigastric and cavernous artery. Nowadays, these techniques are limited to young men with localized obstruction of the internal pudendal artery or common penile artery secondary to trauma. It is a complicated procedure and is not performed routinely.¹⁴

Selection of the source and type of stem cells

For a long time, it was believed that vasculogenesis, the process by which new vessels are formed by endothelial progenitor cells (EPCs), was thought to be restricted to blood vessel formation *in utero*. This dogma was invalidated by the discovery of circulating EPCs by Asahara et al.¹⁵

EPCs are thought to be a subset of cells derived from bone marrow that play a crucial role in neovascularization of ischemic tissue and maintenance of endothelial cell integrity. They can promote adult vasculogenesis and contribute to the recovery of perfusion by homing to, differentiating, proliferating and incorporating into new vessels, producing angiogenic factors, and even through a paracrine effect influencing neighboring cells, thereby

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