

Multipotent Stromal Cell Therapy for Cavernous Nerve Injury-Induced Erectile Dysfunction

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ABSTRACT

Introduction. Erectile dysfunction (ED) following radical prostatectomy (RP) is a result of inadvertent damage to the cavernous nerves that run close to the prostate capsula. The mechanisms behind the development of post-RP ED are increasingly recognized and include cavernosal fibrosis and cavernosal smooth muscle apoptosis, resulting from cavernous nerve degeneration due to neuropraxia. In recent years, cell-based therapies have received increasing attention regarding their potential for recovery of erectile function following cavernous nerve injury (CNI). Multipotent stromal cells (MSCs) are an attractive cell source for this application based on their regenerative potential and their clinical applicability.

Aim. To review available evidence on the efficacy and mechanisms of action of MSC application for the treatment of ED, with an emphasis on ED following CNI.

Methods. A nonsystematic review was conducted on the available English literature between 1966 and 2011 on the search engines SciVerse-sciencedirect, SciVerse-scopus, Google Scholar, and PubMed.

Results. MSCs from both bone marrow and adipose tissue have shown beneficial effects in a variety of animal models for ED. While MSC application in chronic disease models such as diabetes, aging, and hyperlipidemia may result in cell engraftment and possibly MSC differentiation, this observation has not been made in the acute CNI rat model. In the latter setting, MSC effects seem to be established by cell recruitment toward the major pelvic ganglion and local paracrine interaction with the host neural tissue.

Conclusions. While the type of model may influence the mechanisms of action of this MSC-based therapy, MSCs generally display efficacy in various animal models for ED. Before translation to the clinic is established, various hurdles need to be overcome. **Albersen M, Kendirci M, Van der Aa F, Hellstrom WJG, Lue TF, and Spees JL. Multipotent stromal cell therapy for cavernous nerve injury-induced erectile dysfunction. J Sex Med 2012;9:385–403.**

Key Words. Adipose Tissue-Derived Stem Cells; Bone Marrow-Derived Stem Cells; Cavernous Nerve Injury; Recruitment; Erectile Dysfunction; Paracrine

Introduction

Prostate cancer is the most commonly diagnosed and treated solid malignancy in adult males. It has a significant impact on men's health, with 217,730 new cases diagnosed each year and 32,050 annual deaths attributed to the disease in the USA [1]. The lifetime probability of developing prostate cancer is estimated to be 11–20% [2].

In a recent U.S.-based study, 36–41% of men chose radical prostatectomy (RP) to control their localized prostate cancer [3]. Erectile dysfunction (ED) following RP remains a frequent consequence with a significant impact on quality of life in spite of development of novel laparoscopic and robot-assisted operative techniques [4,5]. As prostate cancer is detected at an increasingly younger age and lower stage, patients undergoing RP

generally have better erectile function and have higher expectations concerning the preservation of sexual functioning following treatment. It is recognized that sexual dysfunction is an independent determinant of a reduced quality of life after treatment for prostate cancer [5], whereas maintenance of quality of life is the principle argument in treatment choice for over 45% of patients [6]. It logically follows that an increasing body of research has been focused on understanding the pathophysiology of postprostatectomy ED and the concept of instituting prophylactic measures for prevention and/or early recovery from ED [7,8].

ED following RP is the result of inadvertent injury to the cavernous nerves that run close to the prostate capsule and innervate the corpora cavernosa of the penis. As unassisted nerve regeneration is a slow process, denervation-induced damage, including cavernosal fibrosis and smooth muscle apoptosis in the erectile tissue, frequently develops while the injured cavernous nerve is regenerating [9]. Various research groups have been focusing on how this time frame of nerve regeneration can be shortened and have investigated the effects of neurotrophic factors, type 5 phosphodiesterase (PDE-5) inhibitors, and immunomodulatory molecules in animal models of cavernous nerve injury (CNI) [9]. More recently, cellular therapy has received increasing attention regarding its potential merit for the recovery of erectile function following CNI [10–16]. In this review, we discuss the effects of multipotent stromal cell (MSC) therapy on erectile function, focusing on ED following CNI. Furthermore, we discuss possible mechanisms of action of MSC based on peer-reviewed literature and available research reports.

Methods

An extensive search was conducted on published English language literature between 1966 and 2011 on MSC therapy for the management of ED. The search engines SciVerse-sciedirect, SciVerse-scopus, Google Scholar, and Pubmed were used, with search terms including “ED,” “stem cells,” “MSCs,” “adipose- (tissue-) derived stem cells,” “bone marrow-derived stem cells,” “animal model,” and “CNI.” We opted to focus on recent publications (within the last 10 years) as older publications tended to contain preliminary results that have been more thoroughly or clearly defined in more recent studies. Relevant articles were identified and obtained in full-text form. Abstracts from international meetings were con-

sidered for inclusion only if the data had not been published in manuscript form. Information was critically reviewed and synthesized. Reference lists for several of the manuscripts identified via the search were reviewed and additional relevant citations were obtained from these.

Penile Rehabilitation Therapy and Clinical Need for MSC Therapy

There are a variety of insults to the nerves during RP, including thermal damage, ischemic injury, nerve stretching, and the local inflammatory effects from surgical trauma. Hence, the exact recovery time for return of erectile function after RP is somewhat unpredictable and complete erectile recovery is generally not witnessed until a mean of 18–24 months following surgery [17]. In effect, continued improvement in erectile function is seen beyond 2 years postsurgery [18]. These observations have encouraged clinicians to employ penile rehabilitation practices during the long recovery period.

The clinical strategy of postoperative penile rehabilitation after RP arose from the concept that induced early sexual stimulation and augmented blood flow oxygenating erectile tissue would facilitate the return of unassisted erectile function [19]. An additional (psychological) benefit of early penile rehabilitation after RP is the resumption of sexual activity and improved quality of life [20]. Unfortunately, there is no consensus on the implementation of penile rehabilitation including initiation time, frequency of application, type of vasoactive agents, and dose regimen to be used. After the first report by Montorsi et al. employing intracavernosal alprostadil injections to improve the recovery of spontaneous erections [21], several authors have developed other erectogenic rehabilitation programs utilizing oral PDE-5 inhibitors and vacuum erection devices. A recent prospective study reported greater numbers of men with spontaneous erections and increased responsiveness to oral PDE-5 inhibitor therapy after a regimen consisting of both intracavernosal injections and PDE-5 inhibitors [22]. Based on the available data, either intracavernosal injections and/or vacuum erection device are recommended as first-line options early in the post-RP period, as the mechanism of action does not require intact neural transmission. Thereafter, conversion to PDE-5 inhibitor therapy alone may be an option for men who can achieve at least partial tumescence [19].

In addition to penile rehabilitation protocols, a growing number of studies have employed neuro-

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