

## **Using CD133 stem cells to therapy the erectile dysfunction (ED) by corpus cavernosum angiography surgery.**

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### **Abstract**

**This study reports the treatment effect of CD133 stem cell transplantation using a corpus cavernosum angiographic surgical technique. We recruited 17 volunteers with Erectile Dysfunction (ED). The umbilical cord and peripheral blood stem cells were simultaneously isolated and collected. The peripheral blood stem cells were collected from the patient's biological progeny by mobilization with granulocyte factor. The umbilical cord blood stem cells were collected fresh during the puerperium and shown to be free of blood borne infectious diseases. Then, the mixture of stem cells was transplanted during corpus cavernosum angiographic surgery. All patients who underwent penis vein surgery were followed for 1 year and the changes in clinical symptoms and biochemical indicators were analysed. Seventeen patients with ED were in good health and had a normal sexual life without abnormal reactions or exacerbations. The IIEF-5 scores were >14. This study provided a new method to treat ED with CD133 stem cells, with accurate tissues medical treatment.**

**Keywords:** Erectile dysfunction, Stem cell transplantation, Intracavernosal injection.

*Accepted on March 27, 2017*

### **Introduction**

Herein we report the treatment effect of CD133 stem cell transplantation using a corpus cavernosum angiographic surgical technique. We recruited 17 elderly volunteers with Erectile Dysfunction (ED). The umbilical cord and peripheral blood stem cells were simultaneously isolated and collected. After a 1-year follow-up, 17 patients with ED were in good health and had a normal sexual life, without abnormal reactions or exacerbations. The IIEF-5 scores were >14. This study provides a new method for ED therapy with CD133 stem cells, with accurate tissues medical treatment.

ED is defined as an inability to attain and maintain an erection with sufficient rigidity to have satisfactory sexual intercourse. The elderly are commonly affected due to vascular disease, which is associated with cigarette smoking, aging, diabetes, and hypertension [1]. Thus, we recruited 17 elderly volunteers with ED in the current study. ED increases the economic burden, especially in developing countries [1-3].

Although oral pharmacotherapies, such as phosphodiesterase-5 inhibitors (PDE5is), have benefits, pharmacologic effects are temporary and expensive. Furthermore, pharmacologic agents cannot cure damaged endothelial cells; indeed, oral and local pharmacologic agents provide minimal benefit [4,5].

Consequently, researchers have attempted to use stem cells as a substitute therapeutic strategy for ED. Compared with other treatment methods, the application of cell-based therapy for

ED might be more useful [6-8]. Because stem cells are multipotential cells with self-renewal ability, a small number of stem cells could be effective in diseases involving the vascular wall [6,8].

In the current study, 17 patients were diagnosed with ED in the Department of Urology of Northern Jiangsu People's Hospital (NJPH). All of the patients ranged in age from 55-74 years (average, 62.6 years). The duration of ED ranged from 3-22 years (average, 14 years). Psychological factors were excluded by NJPH.

The international index of erectile function 5 (IIEF-5) was used to assess ED. Seven patients were diagnosed with high-degree ED (score=5-7), and 10 patients were diagnosed with moderate-degree ED (score=8-11).

CD133 is a cell surface molecular marker that is used for isolation and identification of stem cells. Thus, we selected CD133-positive stem cells to treat ED patients in the current study [7,9]. In addition, all patients in the current study were under strict control and were not prescribed male hormones. There are two sources of CD133-positive stem cells. Umbilical cord blood stem cells were collected during the puerperium from healthy parturients without blood borne infectious diseases, including Human Immunodeficiency Virus (HIV), *Treponema pallidum* (TP), hepatitis B virus, and hepatitis C virus. According to the Guidelines of the China National Health Standards for Umbilical Cord Blood Collection, 100 ml of cord blood from normal embryos was collected and a 5-ml

stem cell suspension containing  $2.2 \times 10^7$  was prepared using the Hydroxyethyl Starch Method (HSM).

Peripheral blood stem cells were mobilized with recombinant human granulocyte colony-stimulating factor (rhG-CSF; TeLeJin, Xiamen TeBao Biological Technology Co., Ltd., Xiamen, China) from the biological progeny of elderly males (>18 years of age) for 5 days at a dose of 5 µg/kg/d. Then, 120 ml of mononuclear cells were collected from the donors using COBE 6.1 Spectra Version (Genbro Company, Somerset, New Jersey, USA) on the 6<sup>th</sup> day. CD133 peripheral blood stem cells were separated using a cell sorting reagent (Germany Miltenyi Company, Bergisch Gladbach, Germany) with  $2.2 \times 10^7$  stem cells using a flow cytometry method. Both sources of stem cells were mixed at a 1:1 ratio.

The stem cells were transplanted using a corpus cavernosum angiographic surgical technique. During the operative process, patients were placed in the supine position on the operating table, with local anesthesia by lidocaine. A tourniquet was placed on the root of the penis and 60 mg of papaverine was injected on one side of the cavernosum. Two min later, the tourniquet was removed and the penis was observed for 10 min. Using a high-pressure syringe, 5 ml of the CD133 stem cell suspension was smoothly injected into the corpus cavernosum at 100-180 ml/min. The high-pressure syringe was maintained at <2.0 kPa ml/min to avoid penile erection. Then, compression hemostasis was applied for 10 min after removing the puncture needle.

Biochemical synthesis of citrulline involves two pathways: citrulline is the product of ornithine and carbamyl-phosphate in the urea cycle; and under the catalytic effect of nitric oxide enzyme, arginine is oxidized to N-hydroxyl-arginine, which is again oxidized to citrulline. Nitric oxide is released during this process, which can improve sexual function, resulting in smooth muscle relaxation [10,11].

An Amino Acid Analyzer (AAA) was used to determine the amino acid composition of blood and urine; Gas Chromatography-Mass Spectrometry (GC/MS) was used to determine the organic acids in urine. The two indicators, including citrulline and uric acid, were tested before and after surgery. After detection, although there was a short time in which the Blood Urea Nitrogen (BUN) level was increased, the BUN level decreased slowly to normal in 1 week, which was still <100 µmol/L and comprehensive ED symptoms slowly improved 2 weeks later. Citrulline was at a higher level of growth than arginine. After testing the patients' urine, no meaningful changes in uric acid were detected before and after treatment.

With respect to changes in citrulline and arginine levels, there were significant differences in the blood citrulline level between before and after transplantation ( $F=5.36$ ,  $P=0.004$ ) based on analysis of variance. The results of a paired t-test demonstrated that significant differences existed between them (citrulline and arginine) for 1 year. It should be pointed out that the criteria for abnormal values were citrulline <10 mg/L in blood and uric acid >10 mmol/mol in urine.

In summary, there were 17 patients who received stem cell transplant, and they had a good therapeutic effect after clinical observation. The ED patients had stable vital signs after surgery without tissue necrosis. Only one patient developed a fever after 6 h and 2 patients had abdominal pain 2 hours post-transplantation. These clinical symptoms were relieved 12 h later. There were no secondary infections, no bleeding wounds, and no abnormal reactions following transplantation among the 17 patients. Penile lesions were detected by B ultrasonic wave, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI). No neoplasms or tumor-like lesions were found in the penises of stem cell transplants for 1 year.

During the 1-year of follow-up and medical observation, 17 patients completed IIEF-5 surveys every 3 months. There was a slow increase in their scores. The IIEF-5 scores were >14 by the 6<sup>th</sup> month following treatment, which suggested that the surgical method could improve the quality of their sex life and cure ED.

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